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Effect of music on clinical outcome after hip fracture operations (MCHOPIN): study protocol of a multicentre randomised controlled trial

Victor X Fu ,[1] Johannes Jeekel,[2] Esther M M Van Lieshout ,[3] Detlef Van der Velde,[4] Leonie J P Slegers,[5] Robert Haverlag,[6] Johan Haumann,[7] Marten J Poley,[8,9] Michael H J Verhofstad,[1] on behalf of the MCHOPIN collaborators

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For numbered affiliations see end of article.

Correspondence to
Victor X Fu; v.fu@erasmusmc.nl

ABSTRACT

Background Patients undergoing proximal femur fracture surgery are at high risk of postoperative complications, with postoperative delirium occurring in 25%–40% of patients. Delirium has profound effects on patient outcome and recovery, the patient's family, caregivers and medical costs. Perioperative music has a beneficial effect on eliciting modifiable risk factors of delirium. Therefore, the aim of this trial was to evaluate the effect of perioperative recorded music on postoperative delirium in patients with proximal femur fracture undergoing surgery.

Methods and analysis The Music on Clinical Outcome after Hip Fracture Operations study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Five hundred and eight patients with proximal femur fracture meeting eligibility criteria will be randomised to the music intervention or control group with concealed allocation in a 1:1 ratio, stratified by hospital site. The perioperative music intervention consists of preselected lists totalling 30 hours of music, allowing participants to choose their preferred music from these lists (classical, jazz and blues, pop and Dutch). The primary outcome measure is postoperative delirium rate. Secondary outcome measures include pain, anxiety, medication requirement, postoperative complications, hospital length of stay and 30-day mortality. A 90-day follow-up will be performed in order to assess nursing home length of stay, readmission rate and functional ability to perform daily living activities. Furthermore, the cost and cost-effectiveness of the music intervention will be assessed. Data will be analysed according to an intention-to-treat principle.

Ethics and dissemination The study protocol has been approved by the Medical Research Ethics Committee Erasmus MC on 8 October 2018 (MEC-2018–110, NL64721.078.18). The trial will be carried out following the Declaration of Helsinki principles, Good Clinical Practice guidelines and Dutch Medical Research Involving Human Subjects Act. Research data will be reported following Consolidated Standards of Reporting Trials guidelines and study results will be published in a peer-reviewed journal.

Trial registration number NTR7036.

Strengths and limitations of this study

- This multicentre randomised controlled trial investigating the effects of perioperative recorded music on delirium and postoperative recovery in 508 elderly patients with proximal femur fracture will be conducted in several hospitals in the Netherlands.
- The perioperative music intervention is non-invasive and not associated with any risks or adverse events.
- Due to the profound effects of delirium on patient outcome and recovery, delirium prevention is a quality indicator in healthcare for many hospitals worldwide, making this a clinically relevant trial for a vulnerable patient group with study outcome measures already part of standard patient care, limiting burdening the participating patients.
- Limitations due to lack of blinding related to the music intervention can be justified, as surgical studies and studies evaluating delirium with non-pharmacological interventions can often not be blinded in general.

INTRODUCTION

Proximal femur fractures are common in the elderly and are primarily treated surgically.[1] These frail patients are at a high risk of the occurrence of postoperative complications, as they often have significant comorbidity with polypharmacy use.[2] A prevalent in-hospital complication of the elderly is delirium, an acute, fluctuating, cognitive and consciousness disorder.[3] Postoperative delirium rates in elderly Dutch patients who underwent surgery for proximal femur fracture have been observed to vary between 25% and 40%.[4 5] It has been associated with an increased rate of additional postoperative complications,[6] a prolonged length of hospital stay[6 7] and higher medical costs.[7] Moreover, it has a thorough impact on the

patient's family,[8 9] increasing the risk of poor, long-term functional recovery and mortality rate.[10–12]

As the consequences of experiencing an episode of delirium are profound, delirium is nowadays regarded as a state of acute brain dysfunction.[13] Therefore, there is an increasing interest in delirium prevention and reduction. The exact pathophysiological mechanism of delirium is multifactorial and complex. Primary prevention with non-pharmacological interventions is generally regarded as the most accepted and effective treatment strategy,[3 14] especially since conflicting reports on the effectiveness of prophylactic drug use to prevent delirium have been reported.[15–17] Multiple modifiable precipitating risk factors have been identified.[3 18] These include increased postoperative pain levels[19–21]; higher opioid, sedative and benzodiazepine medication dosages[21–23]; as well as a more vigorous physiological stress response to surgery and elevated stress hormone cortisol level.[3 24] Current patient care aims to reduce these risk factors in order to prevent delirium.

Perioperative recorded music as a non-pharmacological intervention can reduce postoperative pain,[25] intraoperative sedative and postoperative opioid medication requirement,[26] and attenuate the physiological stress response to surgery.[26] Comparisons have been drawn with the most well-known non-pharmacological interventions for surgery, collectively known as the Enhanced Recovery After Surgery protocols, which have the same objectives.[27] Moreover, the music intervention seems to be well liked by patients, with high patient satisfaction levels and willingness to listen to perioperative music again if they were to undergo surgery in the future.[26] The effects of perioperative music on postoperative complications, patient outcome and recovery have only sparingly been investigated,[26 28] with most studies focusing on postoperative pain levels, anxiety or medication requirement in the first few days after surgery. To date, only four small studies in elective knee and hip replacement surgery with sample sizes of 60 patients or less examined the effect of music on confusion and cognitive functioning in adult surgical patients.[29–31] Only two used a delirium screening tool,[32 33] but positive results were reported in all studies.

This multicentre randomised controlled trial will investigate whether perioperative music can reduce the occurrence of postoperative delirium in elderly patients with proximal femur fracture undergoing surgery. Secondary objectives were to assess the effects of perioperative music on pain, anxiety, medication use, postoperative complications, neurohormonal stress response, hospital length of stay, nursing home length of stay, 30-day mortality, 90-day readmission, 90-day functional ability to perform daily living activities, costs and cost-effectiveness.

METHODS AND ANALYSIS

Trial design and setting

The Music on Clinical Outcome after Hip Fracture Operations (MCHOPIN) study is an investigator-initiated, multicentre, randomised, controlled, open-label clinical trial. Patients with proximal femur fracture meeting eligibility criteria will be randomised to the music intervention or control group using a secure web-based, computerised randomisation system with concealed allocation in a 1:1 ratio, stratified by hospital site. Only study staff members and their delegates will have login credentials. The randomisation code for allocation will be kept concealed from the study staff recruiting patients. The music group will receive recorded music as an intervention before, during and after surgery, while the control group will not, but will wear headphones without music during surgery instead. The study will take place in three non-academic hospitals and one academic hospital. Patients will be followed up until 90 days after the proximal femur fracture surgical procedure.

Eligibility, recruitment and consent

Potential eligible patients will be informed about the MCHOPIN study while in the emergency department or on admission to the surgical ward. Information will be provided verbally as well as on paper through a patient information folder with an informed consent form (online supplemental file 1). Patients meeting eligibility criteria and willing to participate will be randomised after written informed consent obtainment. In general, patients with proximal femur fracture will be operated within 48 hours of hospital admission based on guidelines set by the Dutch Healthcare Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg). Therefore, it is not possible to give patients more than a day to consider participation. However, the intervention is non-invasive and not associated with any risks or adverse events.[26] As beneficial effects of music on disruptive behaviour and cognition in patients with dementia have been reported,[34] patients with dementia who underwent surgery for proximal femur fracture are not excluded from study participation, although written informed consent by the proxy is necessary (online supplemental file 2). The information folders for patient and proxy and informed consent forms follow the standard template outlined by the Central Committee on Research Involving Human Subjects, the competent authority for research in the Netherlands and the Dutch Clinical Research Foundation. Patients with hearing aids can also readily participate, which has been consulted with the Erasmus MC Auditory Centre.

Inclusion criteria

1. Patients with a proximal femur fracture undergoing surgical treatment.
2. Age ≥65 years old.
3. Provision of written informed consent by patient or proxy.

Exclusion criteria

1. Additional serious injuries or additional surgical procedures that may affect any of the outcome parameters.
2. Simultaneous bilateral hip fracture.

3. Implant in situ in the affected hip.
4. Severe hearing impairment, defined as no verbal communication possible.
5. Patients unwilling or unable to comply with the intervention.
6. Preoperative planned hospital discharge and return to nursing home within 48 hours of admission.
7. Insufficient knowledge of the Dutch or English language to understand the study documents in the judgement of the attending physician or researcher.
8. Participation in another intervention study that might influence the duration of surgery or any of the outcome parameters.

Primary outcome

The primary outcome measure is postoperative delirium. Participating patients will be screened using the Delirium Observation Screening (DOS) scale, a diagnostic nursing screening tool. The DOS scale is a 13-item scale facilitated in order to recognise delirium early, with valid consistency and reliability in both geriatric patients and elderly patients with hip fracture.[35 36]

The DOS end score is the sum of the three DOS scales, assessed during each shift by the nurse, divided by 3. A DOS end score ranges between 0 and 13. In a study of 92 patients with hip fracture, a DOS end score of 3 or more had a 94.4% sensitivity of delirium, while a score less than 3 had a 76.6% specificity.[35 36] Because the DOS scale is easy to use, requires no active patient participation and has been validated in several trials,[37 38] it is a standard part of multidisciplinary delirium prevention measures in patients with proximal femur fracture in the Dutch National Guidelines on delirium. In case of a DOS end score of 3 or more, the geriatrician will be consulted for patient assessment to confirm clinical diagnosis of delirium using the *Diagnostic Statistical Manual*, Fourth Edition, criteria. These criteria define delirium as an acute, fluctuating disturbance of consciousness with inability to focus and shift of attention, caused by a general medical condition. In all participating hospitals, a geriatrician is part of and actively involved in the proximal femur fracture surgery patient care team.

Secondary outcomes

Secondary outcome measures are

- Postoperative pain, assessed using an 11-point Numerical Rating Scale (NRS), in which 0 implies no pain and 10 implies the worst pain possible.
- Anxiety, assessed using the Six-Item State-Trait Anxiety Inventory (STAI-6).[39] Feelings of anxiety are reported on a 4-point Likert scale for each item, with a score between 20 and 80 points for each questionnaire. Scoring is achieved by reverse scoring the three positive items, summing all six scores and multiplying the total score by 20/6. A higher score correlates to a higher level of anxiety. The State-Trait Anxiety Inventory (STAI), consisting of two 20-item subscale questionnaires, is one of the most frequently used anxiety questionnaires in clinical research.[40] The state subscale measures situation-related anxiety, anxiety at the very moment, while the trait subscale measures disposition-related anxiety, anxiety as a general personal characteristic trait. A major drawback of the STAI is its length, especially in a study population of elderly patients with frequent cognitive impairment, pain and opioid requirement. In order to increase compliance and minimise unanswered items, the six-item short form of the STAI state by Marteau and Bekker will be used.[39] The STAI-6 has a high internal reliability and correlation with the full-form STAI,[39 41 42] has been used in clinical research in elderly patients[43 44] and has been validated in Dutch.[45]
- Medication use, consisting of intraoperative and postoperative opioid medication, as well as postoperative benzodiazepines and postoperative antipsychotic medication for the treatment of delirium. Data will be collected from the electronic patient file. Analgesic opioid medication will be converted to milligrams of morphine equivalents (1 mg ME=1 mg parenteral morphine).
- Postoperative complication rate. Data will be collected from the electronic patient database and classified according to the Clavien-Dindo classification.[46]
- Neurohormonal stress response, assessed by measuring serum cortisol. An increased stress response after surgery has been associated with an increased risk of postoperative delirium.[24] The duration until peak cortisol level depends on the surgical severity and is an indicator of intrinsic physiological stress.[47] Peak levels of cortisol are observed 4 hours after start of surgery in moderate and after 8 hours in major surgical procedures. Proximal femur fracture surgery is generally classified as a major surgical procedure. Therefore, the second serum cortisol will be drawn 6 hours after the first sample. This will be combined with the blood draw postoperatively for the postoperative serum haemoglobin measurement, which is part of standard surgical care.
- Hospital length of stay in days, as calculated from the hospital admission date until declared 'medically ready for discharge' by the attending physician as recorded in the patient's medical file. Also, the full length of stay until the actual discharge from hospital will be assessed.
- Thirty-day mortality, as calculated from the date of admission.
- Nursing home length of stay in days, as calculated from nursing home admission date until discharge.
- Ninety-day readmission, as calculated from the date of admission.
- Ninety-day functional ability to perform daily living activities, which will be assessed during standard postoperative outpatient visit 3 months postoperatively using the Katz Index of Activities of Daily Living (Katz-ADL6). This six-item instrument assesses basic activities of daily living in six functions, with a total

score of 6 indicating full function and a score of 2 or less indicating severe functional impairment.[48]

- Through an economic evaluation, the cost-effectiveness of the music intervention will be investigated using the method of cost-effectiveness analysis (CEA). The evaluation will be conducted from a healthcare perspective, with a time horizon of 90 days. It will make a comparison between the intervention and the control group by identifying, measuring, and valuing the costs and patient outcomes of both treatment strategies. The costs will include costs of the initial hospital admission (either on the ward or on the intensive care unit), primary surgery and additional procedures (including surgical reinterventions), medications, diagnostic imaging, in-hospital consultations, and costs for headphones and sound equipment. The analysis will take into account costs after hospital discharge, including costs of outpatient consultations, visits to the emergency room, consultations with the general practitioner, home care and nursing home admissions. Data on resource consumption will be collected from the electronic patient database and using a custom follow-up questionnaire. These data will then be combined with unit costs to generate patient-level costs. Costs of productivity losses will be ignored in this study, because these are expected to be minor, given the age range of the patients. Regarding patient outcomes, the CEA will consider the occurrence of delirium (as defined above). An incremental cost-effectiveness ratio (ICER) will be calculated as the difference in cost between the two treatment strategies divided by the difference in effectiveness, unless one treatment dominates the other (ie, has lower costs and greater effects). This ICER will be expressed as incremental costs per case of delirium prevented.

Additional study parameters assessed will be patient demographic characteristics, preoperative medication use, medical and surgical patient history, living situation prior to hospital admission, education level, injury and treatment characteristics, and music preferences and its importance in daily life. Cognitive functioning, a prominent risk factor for delirium,[49] will be screened preoperatively using the Mini-Cog, a three-item screening questionnaire with high correlation to cognitive functioning assessment by the Mini-Mental State Examination.[50 51]

Study intervention

The music group will listen to music preoperatively, intraoperatively and postoperatively during the first 5 days after surgery. The preoperative music intervention will be ideally at least 15 min, as a relatively short exposure time seems to already have an effect.[26] The intraoperative music intervention will start after anaesthesia induction until the patient chooses to remove the headphone in the recovery room. Postoperatively, the music group will listen to music two times per day for 30 min, starting from the first until the fifth postoperative day or until patient discharge. Previous studies have reported noise levels exceeding 100 decibels adjusted during surgery.[52] Noise pollution during surgery is possibly associated with a negative effect on patient outcome,[53] with higher noise levels reportedly increasing postoperative complications rate and stress hormone levels.[54–56] Therefore, the control group will receive standard patient care and in addition wear headphones intraoperatively without music in order to avoid possible criticism that the observed effects are solely due to noise reduction and not through music. Before and after surgery, noise levels are generally quite lower compared with during surgery.[53] A recent study reported that awake patients might have increased anxiety due to wearing headphones,[57] which is also the reason why noise-cancelling headphones blocking all ambient noise are not used.

The music intervention consists of preselected music divided in four playlists (classical, jazz and blues, pop and Dutch music) providing approximately 30 hours of music using a tablet. Patients are allowed to choose music from these list, as the largest beneficial effects were previously observed when patients selected music from a preselected playlist.[25] Moreover, it is unlikely that patients with a proximal femur fracture admitted through the emergency department after transport by ambulance will bring their own favourite music. Music was selected by a panel of five research physicians with extensive knowledge of perioperative music, based on literature recommendations and music used in previous studies. Care was taken to choose popular music from the patients' youth and early adulthood (50s–80s) which would likely be familiar to the patient, as a familiar environment can reduce the occurrence of delirium.[58] Consent was obtained from the music copyright managing organisations in the Netherlands, Buma Association and Stemra Foundation (Dutch: Vereniging Buma and Stichting Stemra), to use recorded music for study research purposes.

The Lenovo Tab E7 16 GB and disposable HP 112 Fetum medically approved headphones will be used as music devices, along with the free AIMP audio player, which are easy to use and require minimal effort to select the preferred music list. The tablet also allows for magnification in order to assist visually impaired participants to choose the music.

Study procedures

A timeline detailing study procedures and outcome measures is presented in figure 1. After signing informed consent and computerised randomisation, the Mini-Cog will be administered and baseline NRS for pain and STAI-6 will be filled out also by all participants, followed by preoperative geriatric consult and DOS scores as part of standard care. A custom-made demographic questionnaire on preoperative living situation, education level and music will be provided as well.

The preoperative music intervention for the music group will start from the surgical ward when the patient

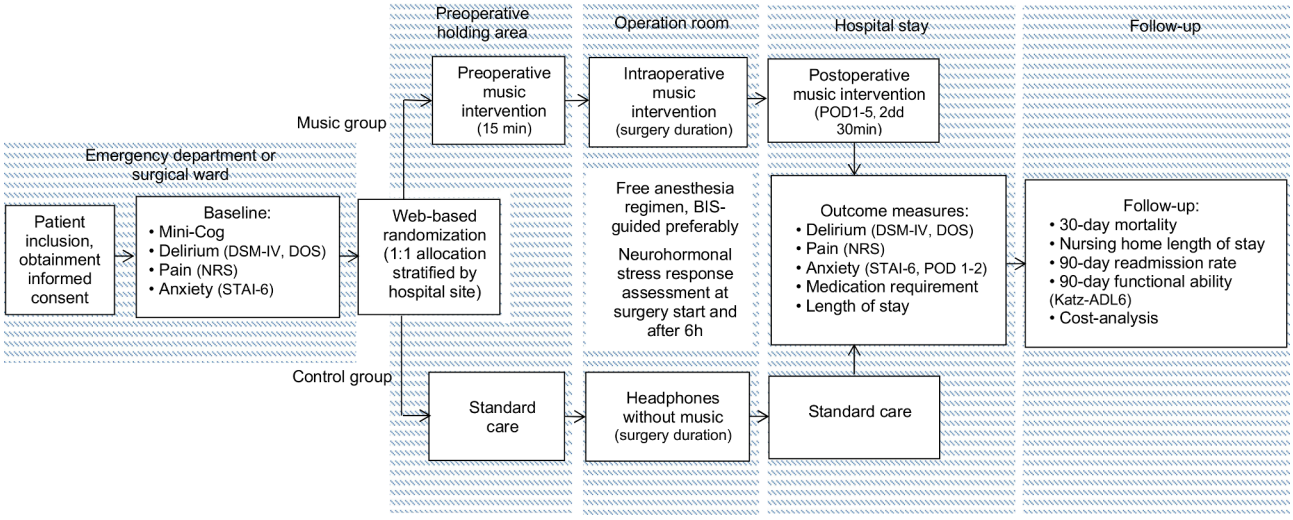

Figure 1 MCHOPIN study overview detailing study procedures. The music intervention consists of approximately 30 hours of preselected music divided in four playlists (classical, jazz and blues, pop and Dutch music), allowing patients to choose from these lists. BIS, Bispectral index; DOS, Delirium Observation Screening; DSM-IV, *Diagnostic Statistical Manual*, Fourth Edition; Katz-ADL6, Six-Item Katz Index of Activities of Daily Living; MCHOPIN, Music on Clinical Outcome after Hip Fracture Operations; NRS, Numerical Rating Scale; POD, Postoperative day; STAI-6, Six-Item State-Trait Anxiety Inventory.

is called up for surgery and continue until arrival in the operating room, whereas the control group will receive standard care preoperatively. The anaesthesiologist and surgical team will be free to decide whether general or locoregional anaesthesia will be used, as well as the anaesthesia regimen, reflecting daily clinical practice. Beneficial effects of music on postoperative pain and opioid requirement have been observed during both general and locoregional anaesthesia,[26] even when music is solely played intraoperatively when compared with headphones without music.[59] Preferably, anaesthesia administration will be guided by using a bispectral index monitor or comparable anaesthesia depth monitoring device. While a recent meta-analysis reported that significantly less propofol is needed to reach the same sedation level measured using bispectral index when listening to music intraoperatively, the majority of hospitals employ volatile anaesthesia for sedation regarding proximal femur fracture surgery. Therefore, the intraoperative sedative dosages are not recorded. After induction, the first cortisol blood sample will be drawn and all subjects will receive headphones. The control group will wear headphones in order to assess the music intervention and not noise reduction. All participants will wear headphones until arrival in the recovery room, where they can chose to remove them when they wish. No corticosteroids will be administered between the first and second cortisol blood sample drawing (6 hours after the first blood sample), unless this is deemed clinically necessary by the patient care team. As previously mentioned, cortisol will not be assessed in a selected group of patients participating in his trial.

For all participating patients postoperatively, the DOS will be assessed three times per day, with the geriatrician actively involved in proximal femur fracture surgery patient care. The NRS for pain will be assessed daily and postoperative opioid dosage will be administered based on the NRS and care team observations. The STAI-6 will be filled out by all participants during the first and second postoperative days. Data on the NRS for pain, DOS, postoperative medication requirement, postoperative complication rate, hospital length of stay and 30-day mortality rate will be retrieved from the electronic patient database. All participants will be followed up until 3 months postoperatively. Two questionnaires, the custom-made follow-up questionnaire and the Katz-ADL6 questionnaire, will be administered during either the outpatient follow-up visit or by phone. The follow-up questionnaire will assess nursing home length of stay, 90-day readmission rate and information needed for the economic evaluation.

Sample size calculation

Literature on the frequency of postoperative delirium in patients with proximal femur fracture who underwent surgery varies between 15% and 60%,[2] with a recent meta-analysis reporting an accumulated prevalence of 24%.[60] Delirium in Dutch proximal femur fracture surgery patients over 65 years of age has been observed in 19%–37% of patients.[61 62] Previously, a meta-analysis assessing effectiveness of different, mostly non-pharmacological interventions reported a reduction in delirium rates of 13%.[63] In order to assess a minimally clinical relevant reduction of 13% in delirium frequency when taking 15%–60% of delirium into account, with a power of 80%, alpha of 5% and planned two-sided testing, taking into account possible in-hospital mortality and loss-to-follow-up of 10% overall, 508 patients should be enrolled (254 per group).

Data collection and management

Clinical research assistants will be available at participating hospital sites to assist in executing study procedures and

data collection. Research data will be collected using questionnaires and with a case report form with data from the electronic patient database. The handling of personal data will comply with the Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming). Research data will be stored electronically in a database with an audit trail that meets Good Clinical Practice standards (OpenClinica) and will be handled confidentially. Any information on paper collected during this study will be placed in a research folder, which will be filed in locked cabinets in research offices at the participating hospitals. Data will be stored during the study period and for a period of 15 years after completion of the study.

Monitoring, safety and auditing

An appointed monitor will develop standard procedures and details on the monitoring activities. The sponsor/investigator has a liability insurance which is in accordance with the Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch Wetenschappelijk Onderzoek met Mensen (WMO)). The Medical Research Ethics Committee Erasmus MC has given dispensation from the statutory obligation to provide insurance for subjects participating in medical research, as participation in this study is considered to be without risks.

No deleterious or negative adverse side effects associated with listening to music as a perioperative intervention are known.[26] In accordance, the investigator will report all serious adverse events to the sponsor, except for the specific serious adverse events which are considered not related to the music intervention and common in patients with proximal femur fracture who underwent surgery. A maximum sound level will be ensured to prevent hearing damage. The headphones and sound equipment will be cleaned with a damp microfibre cloth and the ear pads or buds will be replaced after use by the patient during hospital stay, in order to reuse the devices, in accordance with the Erasmus MC Infection Prevention Unit and local hospital protocols. No additional or enhanced hygiene measures will be needed concerning the use of headphones and sound equipment in the operating room complex and the same sound equipment set will be used on the ward.

Statistical analysis

Data will be analysed using the Statistical Package for the Social Sciences V.24.0 or higher. Normality of continuous data will be tested with the Shapiro-Wilk test. Homogeneity of variances will be tested using Levene's test. A two-sided p value of <0.05 will be taken as threshold of statistical significance in all statistical tests. The analyses will be performed on an intention-to-treat basis. Should there be 5% crossovers, a per protocol analysis will also be done. If necessary, missing values will be replaced using multiple imputations following the predictive mean matching method, using 10 imputations.

Descriptive analysis will be performed in order to report the outcome measures for both treatment groups. For continuous data, the mean and SD (parametric data) or the median and percentiles (non-parametric data) will be reported per treatment group. For categorical data, numbers and frequencies will be reported per treatment group. The only exception is that costs will be reported as mean with 95% CI. The 95% CI around the mean costs will be approximated by non-parametric bootstrapping. Continuous data will be tested using Student's t-test or the Mann-Whitney U test, as appropriate. Categorical data will be tested using the χ^2 or Fisher's exact test, as applicable. Both univariable and multivariable analyses will be performed. A binary logistic regression model (for binary outcomes) or multivariable linear regression model (for continuous outcomes) will be developed, with the outcome as dependent variable and the study group (ie, intervention or control) as covariate. Patient, injury and treatment variables that differ between the groups and may confound the association of the intervention and outcome will be entered into the model. Variables will be entered into the model if univariate analysis produces a p value of 0.05 or lower. The unadjusted and adjusted ORs (for binary outcomes) and beta values (for continuous outcomes) will be reported with 95% CI. A subanalysis for all outcome measures will be performed by stratifying patients according to their age (<80 and ≥80 years).

Blinding

Patients enrolled in the MCHOPIN study will not be blinded to the music intervention. While the surgical team will be blinded intraoperatively on paper as all patients will wear headphones during surgery, in practice, it will not be possible to blind the surgical team as patients can adjust the music volume or ask for a different playlist while in the operating room or postoperatively on the surgical ward. The clinical chemist and laboratory site concerned with the analysis of the neurohormonal cortisol stress response samples will be blinded to the intervention. Also, a part of the statistical analysis, which includes the primary and almost all of the secondary outcome measures except the economic analysis, will be performed by a statistician blinded to the music intervention.

Patient and public involvement

Neither patients nor the public was involved in the study design, recruitment to and conduct of the study, nor in assessing the burden of the intervention.

ETHICS AND DISSEMINATION

This study will be conducted in accordance to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, 2013) and in accordance to the Medical Research Involving Human Subjects Act (in Dutch: WMO). Written informed consent will be obtained from each patient or proxy.

Ethics approval and trial registration

Approval by the Medical Research Ethics Committee Erasmus MC was obtained on 8 October 2018 (MEC-2018–110 and NL64721.078.18). Local approval in the participating hospitals followed suit and the study was open for inclusion starting from 5 March 2019. The trial protocol has had no substantial amendments to the original protocol. This trial has been registered in the Dutch Trial Register.

Dissemination policy

Research data will be reported following the Consolidated Standards of Reporting Trials guidelines.[64] No research data that can be traced to individual persons will be presented or published. On completion of the trial, the research team aims to publish the manuscript in a peer-reviewed journal and present results in national and international conferences. Each participating hospital will be invited to provide coauthors for a collaborator group authorship consisting of one trauma surgeon and one anaesthesiologist, provided that 15% of the total required study sample size is included at that site. All participating hospitals will be acknowledged for their participation.

DISCUSSION

Delirium is a prevalent complication in in-hospital elderly patients and is associated with prolonged hospitalisation due to an increased risk of postoperative complications and mortality. It also leads to long-term cognitive and functional impairment.[3 6 7 10 11] Therefore, an increasing research interest in delirium prevention and treatment has developed over the past two decades. Delirium prevention is currently a healthcare quality indicator in many countries worldwide.[65] Several non-pharmacological multimodal intervention programmes have reported beneficial results on reducing delirium,[3 16] especially since the pharmacological prevention and treatment of delirium remain somewhat controversial.[3 16 17 66] Given the multifactorial factors involved in delirium development, current guidelines consist of both multimodal pharmacological and non-pharmacological interventions. While no clinical useful biomarker for delirium has currently been identified yet,[67] serum cortisol reportedly has delirious effects when increased.[68–71] It has been theorised that overstimulation of the hippocampus, rich in glucocorticoid receptors and therefore susceptible for cortisol and stress, plays a role in delirium development.[72] Given that perioperative music can attenuate the neurohormonal cortisol stress response,[26] combined with the significant beneficial effects of perioperative music on postoperative pain, anxiety, intraoperative sedative requirement and postoperative opioid usage,[25 26] the multicentre, randomised controlled, clinical MCHOPIN trial will assess the effect of perioperative recorded music on postoperative delirium, patient outcome and recovery in elderly patients with proximal femur fracture who underwent surgery.

An exhaustive literature search with a biomedical information specialist was performed on 16 October 2020 in order to assess current literature on perioperative music and postoperative delirium in adult surgical patients. Only four randomised controlled trials evaluated the effect of music on postoperative cognitive functioning and delirium. McCaffrey and Locsin *et al* reported significant lower acute confusion episodes in two trials with 190 elderly patients undergoing elective hip or knee surgery.[30 31] However, confusion was ascertained by reading the nurse's narrative notes without use of screening tools for delirium recognition. Two other studies observed significantly lower rates of postoperative acute confusion ascertained using the validated NEECHAM Acute Confusion Scale when patients listened to music postoperatively compared with standard care. Sample sizes were relatively small, with only 22 and 60 patients who had elective hip and knee surgery included.[32 33]

In the MCHOPIN study, the DOS score will be used to proactively screen for delirium in all participants during each nursing shift.[35 37] Given that delirium is often not recognised or misdiagnosed, a strong point of this trial is that all participating hospitals are high-volume centres which actively involve the geriatrician in the care of all admitted proximal femur fracture surgery patients. Both patients and practitioners will not be blinded, as the beneficial effects of perioperative music seem largest when music is applied before, during and after surgery instead of only intraoperatively during general anaesthesia.[25 26] Also, a significant portion of patients with proximal femur fracture who underwent surgery are operated on while receiving locoregional anaesthesia.

We believe it acceptable that no blinding is applied, as patients cannot be blinded in many surgical trials. Only 3% and 37% of practitioners and patients were blinded in high-impact surgical randomised controlled trials.[73] Moreover, primary prevention of delirium is generally accepted to be most effective with non-pharmacological interventions,[3] meaning blinding is not possible. The anaesthesiologist and surgical team will be free to decide the manner of anaesthesia and perioperative analgesia regimen. Given the number of patients who will be enrolled in this trial and the stratification per hospital site, it is assumed that this will balance itself out and no differences in locoregional or general anaesthesia and analgesia medication will be observed between the intervention and the control groups.

To our knowledge, this is the first large, multicentre randomised controlled trial investigating the effect of perioperative recorded music on postoperative clinical patient outcome and recovery which also employs a reasonable follow-up time after patient discharge. Moreover, only a limited number of studies evaluating perioperative music involved acute care or elderly surgical patients. Perioperative recorded music is an attractive intervention specifically in this patient group as it is safe, well liked, and reduces sedative and opioid medication requirements.[26] The study population of patients

undergoing proximal femur fracture surgery was chosen because of the prevalent occurrence of postoperative delirium and high levels of postoperative pain and stress. Results of this trial will give insight in reduction of delirium in a prevalent and vulnerable patient group, as well as clarify the relation between neurohormonal stress response to surgery activity, the occurrence of delirium and postoperative complication rate.

TRIAL STATUS

The current protocol is V.3.0, dated 15 August 2018. The first patient was included on 5 March 2019, and inclusion was originally expected to continue until December 2021 at time of inception, but is now projected to continue until 2022. The study is open for patient inclusion.

Author affiliations
[1]Trauma Research Unit, Department of Surgery, Erasmus MC, Rotterdam, The Netherlands
[2]Department of Neuroscience, Erasmus MC, Rotterdam, Netherlands
[3]Trauma Research Unit, Erasmus MC, Rotterdam, The Netherlands
[4]Department of Surgery, Sint Antonius Ziekenhuis, Utrecht, The Netherlands
[5]Department of Anaesthesiology, Sint Antonius Ziekenhuis, Utrecht, The Netherlands
[6]Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[7]Department of Anaesthesiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[8]Institute for Medical Technology Assessment, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands
[9]Department of Pediatric Surgery and Intensive Care, Erasmus MC, Rotterdam, The Netherlands

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ORCID iDs
Victor X Fu http://orcid.org/0000-0002-0029-0816
Esther M M Van Lieshout http://orcid.org/0000-0002-2597-7948

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