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Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study

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ABSTRACT

Introduction In the early weeks after surgery, patients may experience cognitive changes and impaired memory and concentration—changes commonly referred to as postoperative cognitive decline. It is often the patient and/or a relative that initially detects a change in cognitive capacity after surgery, typically when resuming daily activities. We lack information about how patients experience early postoperative cognition (*delayed neurocognitive recovery*) and if these experiences can be reflected in biochemical pattern of inflammatory signalling molecules, cognitive function as well as on quality of postoperative recovery.

Methods and analysis The study has a mixed-methods design that is integration of qualitative and quantitative data within a single investigation. Participants included will be patients aged ≥60 years that are undergoing major elective joint replacement surgery (n=40) and their relative. Patient's experience of his/her early cognition will be captured by interviews on postoperative day 13–16 during the follow-up visit. A relative will also be interviewed on the same day or the day after. Cognitive function will be measured preoperatively and on postoperative day 13–16 using the International Study Group of Postoperative Cognitive Dysfunction test battery. Symptoms/discomfort will be measured preoperatively and postoperatively (on postoperative day 1 and 2 and at the follow-up visit day 13–16) by the Swedish version of Quality of Recovery and by a visual analogue scale assessing pain intensity. Biomarkers will also be collected at the same time points. The findings from the interviews will be sorted out depending on group stratification (no delayed neurocognitive recovery and delayed neurocognitive recovery). The qualitative and quantitative findings will be compared to seek for similarities and differences.

Ethics and dissemination The project has been approved by the Swedish Ethical Review Authority (2019–02968) and will follow the principles outlined in the 1964 Helsinki Declaration and its later amendments. Results from this study will be disseminated in peer-reviewed journals, scientific conferences and in social media.

Strengths and limitations of this study

- A mixed-methods study comparing patients' experiences of early postoperative cognition with patterns in biochemical pattern of inflammatory signalling molecules, cognitive function assessed with validated neuropsychological tests as well as on quality of postoperative recovery.
- Patients' own experiences of early postoperative cognition including their relative's view have never been reported earlier.
- This study includes a small sample of patients and is conducted in Sweden, and may not be generalisable to other contexts.

INTRODUCTION

Postoperative neurocognitive decline (POCD, previously termed postoperative cognitive dysfunction) is one of the the most common complications after otherwise uneventful surgery and affects multiple cognitive domains such as memory, executive functions, information processing speed and attention[1–5] with subsequently impaired day-to-day memory, language skills, attention and learning compared with levels demonstrated preoperatively.[6] Postoperative cognitive decline is diagnosed up to 30 days postoperatively (*delayed neurocognitive recovery*)[7] and is a subtler deterioration in cognition, as it is not characterised by obvious clinical symptoms such as a change in the level of consciousness.[8] With advanced age as the primary risk factor for neurocognitive decline,[2 4 5 8–10] the incidence of cognitive dysfunction in elderly patients 1 week after surgery is approximately 25%[2 9–11] and remains at 10% at 3 months.[2 9 10] Intraoperative factors have been hypothesised as playing a role in the occurrence of POCD. Yet, choice of anaesthesia (general vs regional) has not been found to influence

development of POCD[8 12 13] as well as the choice of anaesthetic agent,[14] depth of anaesthesia[15] and intraoperative hypotension.[16]

While the mechanism behind postoperative neurocognitive disorders are not fully uncovered, there is a growing body of evidence that surgery-induced inflammation spread systemically via blood-borne immune cells and cytokines to the brain via a disrupted blood-brain barrier, resulting a transient neuroinflammation with impaired cognitive processing.[17 18] It has been reported an inflammatory response to surgical procedure has significant involvement in the POCD development.[11] This postoperative neuroinflammatory reaction can be altered by multiple factors within the perioperative period such as pain, sleep disturbances and prolonged infection.[6]

Because clinical evaluation of the brain is not a routine part of preoperative evaluation[19] and the discrete nature of cognitive disorders, it is often the patient and/or a relative who in the first instance detects a change in cognitive capacity after surgery, typically when resuming daily activities.[5] It has also been reported that elderly patients are 'never the same' after surgery.[12] Evidence suggests that neurocognitive decline can act as a precursor of significant functional impairment following surgery; patients developing neurocognitive decline leave the labour market early and are more dependent on social transfer payments.[20] Neurocognitive disorders are, furthermore, associated with increased mortality[3 20] and with prolonged hospitalisation.[4] Evered *et al* proclaim that perioperative cognition has become largely a research area rather than a clinical state meaning that subjective aspects are rarely sought or reported as well as capacity for activities of daily living is overlooked. Therefore, a subjective report from the patient is an essential element of diagnosing a perioperative neurocognitive decline.[7]

Aim

The aim of present study is therefore to explore patients' experiences of their early postoperative cognition after major orthopaedic surgery in relation to postoperative cognitive function assessed with validated neuropsychological tests, inflammatory signalling molecules and quality of postoperative recovery as well as to describe the relative's view of early postoperative cognition.

METHODS AND ANALYSIS

Study design

A mixed-methods study that is inductive concurrent design where the core component is qualitative and the supplemental component is quantitative with integration of qualitative and quantitative data within a single investigation[21 22] will be undertaken to address the research questions. Study recruitment started in October 2019 and is planned to end in April 2020.

Participants

Patients

Participants included will be patients undergoing major elective joint replacement surgery (n=40) at a university hospital in Sweden. The sample size is based on the mixed-methods study design and the incidence of early cognitive decline at 1–2 weeks postoperatively of 17%–25%.[2 23] However, unpublished research with new reference values indicates that the incidence is underestimated, and instead up to 50% can suffer from POCD.

Exclusion criteria: a score on the Mini-Mental State Examination (MMSE) at screening of ≤22, that is, suspected dementia[24]; <60 years of age; suffering from a nervous system disease; taking tranquillisers or antidepressants; underwent a surgical procedure in the previous 6 months; inability to read and speak Swedish or suffering from a severe visual or auditory disorder, alcoholism or drug dependence.

Relatives

One close relative (spouse or children with age ≥18 years) per patient will be asked to participate. Inclusion criteria for the relatives included identifying themselves as being a relative whom the patient included in the study and being able to take part in an interview in Swedish. The patient decides which relative should be asked. If the relative does not accept to be included, the patient will not be excluded.

Recruitment

One of the researchers will, during their preoperative anaesthesia consultation, provide oral and written information about the study. The details of the study and its potential benefits as well as risks will be explained thoroughly to the patient. If the patient agrees to participation in the study, they will undergo the MMSE screening. Values >22 indicated that the patient is eligible to participate (figure 1).

Qualitative data

Interviews

The patients and their relative will be interviewed separately. The opening question to the patients is: *"How do you yourself experience the time after the operation compared to before?"* Opening question to the relative: *"How would you describe your relative regarding being as they used to be, being themselves, before the operation compared to the time after surgery"*. Probing questions were asked such as *"What do you mean?"* and *"How would you describe that?"* The informants will be encouraged to speak freely about the experience. An interview guide will be used to ensure covering issues such as cognition, memory loss, attention, mood and daily activity.

Quantitative data

Cognitive testing

Cognitive function will be measured preoperatively and on postoperative day 13–16 using the International Study Group of Postoperative Cognitive Dysfunction (ISPOCD)

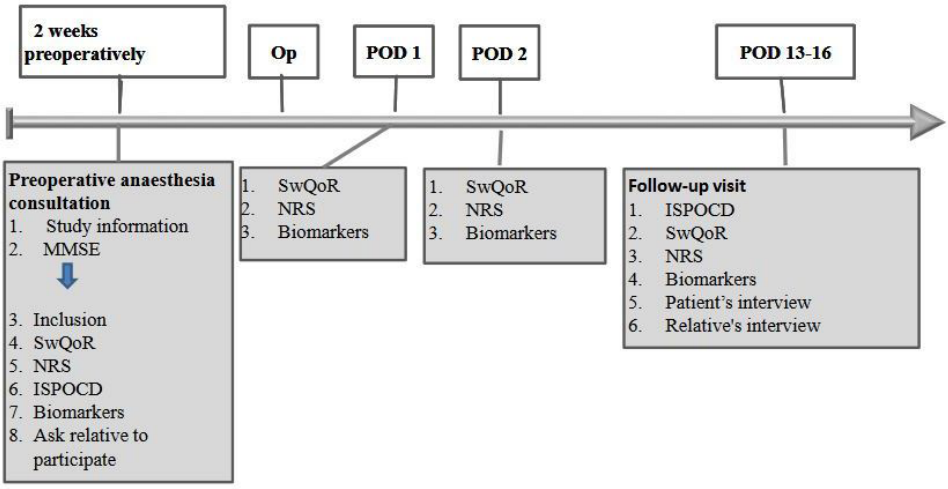

Figure 1 Overview of the research process. ISPOCD, International Study Group of Postoperative Cognitive Dysfunction; MMSE, Mini-Mental State Examination; NRS, numerical rating scale; POD, postoperative day; SwQoR, Swedish version of Quality of Recovery.

neuropsychological test battery. The ISPOCD battery assesses cognitive performance using four different tests, providing seven variables for analysis, including Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Colour-Word Test, the Letter-Digit Coding Test[2] and has been validated in the perioperative setting for two decades.[6] The tests will be administered in the same sequence at each test session by the same researcher following a standardised instruction manual in order to ensure as uniform a test situation as possible. The tests will be carried out in quiet rooms and only the patient and a researcher (KL) will be present.

Blood-borne biomarkers

Inflammatory signalling molecules such as C reactive protein, interleukin 1-beta, interleukin-6, interleukin-10, High Mobility Group Box 1 (HMGB-1) and fractalkine will be measured preoperatively and postoperatively. Venous blood samples (20 mL whole blood) will be drawn from an intravenous cannula. Blood will be centrifuged and plasma stored at −80°C until further analysed.

Quality of recovery

The patients' quality of recovery will be measured by the Swedish version of Quality of Recovery (SwQoR), which measures 24 different items related to symptoms/discomfort that appear postoperatively, such as pain, anxiety, sleep difficulties, dizziness, fatigue, returning to work or usual home activities. The items are rated on 11-point numerical scales ranging from 0, 'none of the time', to 10, 'all of the time'. Reliability and validity tests have provided evidence that it is appropriate to use SwQoR in patients undergoing surgery.[25]

Pain intensity

Pain intensity will be measured using a numerical rating scale (NRS) from 0=no pain to 10=maximum possible pain. The NRS has been tested for reliability and validity in a Swedish population.[26]

Demographic and perioperative data

These include: age, sex, MMSE score, comorbidities, American Society of Anaesthesiologists classification, aesthetic technique and duration, duration of the procedure, blood loss (mL), blood transfusion (mL), use of analgesics during hospitalisation and at home until the follow-up visit, postoperative complications and length of stay.

Procedure

Preoperative data collection

If the patient chooses to participate in the study, they will undergo the cognitive test preoperatively. The test will be performed in an undisturbed room where only the patient and researchers will be present. The tests are expected to take about 20 min. Blood-borne biomarkers will be collected and SwQoR and pain intensity questions will be measured after the cognitive testing is completed (table 1 and figure 1). The day and time of day for preoperative data collection will be documented.

Postoperative data collection

The cognitive test and the interview with the patients will take place on postoperative day 13–16 during the patient's follow-up visit. After the cognitive test is completed, SwQoR and biomarkers will be measured. The patient's relatives will be interviewed separately on the same day or the day after and by the same researcher (KL). All cognitive tests will be performed by one of the researchers from the research group (KL), with education and experience of performing the test. SwQoR, pain intensity and blood-borne biomarkers will be measured postoperative day 1–3, the same time of day ±2 hours and on day 13–16 during patient's follow-up visit. The day and time of day for sampling biomarkers at the follow-up visit will be documented. A research nurse at the Clinical Research Unit at the University Hospital will collect all biomarkers (table 1 and figure 1).

Table 1 Outcome measures

Outcome		Preoperative	POD 1	POD 2	POD 13–16
Cognitive test	ISPOCD battery	X			X
Neuroinflammatory reaction	Blood-borne biomarkers	X	X	X	X
Postoperative recovery	Swedish version of Quality of Recovery questionnaire	X	X	X	X
Pain intensity	Numerical rating scale	X	X	X	X
Experiences of postoperative cognition	Interviews with patients and relatives				X

ISPOCD, the International Study Group of Postoperative Cognitive Dysfunction; POD, postoperative day.

Data analysis

Qualitative data analysis

All interviews will be transcribed verbatim and analysed in line with an inductive thematic analysis.[27] In the first step, all interviews will be read through, patients and relatives separately, and expressions concerning the experienced postoperative cognitive decline will be marked. At the same time, initial reflections on the data will be noted. In the second step, the marked expressions will be coded into a condensed, semantic description of the experiences expressed. Third, themes will be identified, based on sorting the codes and initial reflections. In this step, relations between and levels of the themes will also be mapped. In step four, a review of the themes will be conducted, in which all codes included in a theme are considered, following which the whole analysis is considered in relation to the initial reflections and original texts. Thereafter, all themes and subthemes will be named. The findings from patients and relatives will be presented separately as well as being compared to seek for similarities and differences, and will be highlighted. Also, individual similarities and differences within the couples will be presented. The data analysis will be blinded to the findings from the biomarkers, cognitive tests, SwQoR and pain in order to not be influenced. The analysis will be performed in Swedish and thereafter be translated into English.

Quantitative data analysis

Changes in cognitive performance will be calculated for each of seven test variables and corrected for practice effects and variability using data from a historical age-matched control group that has undergone testing using the same battery and with the same intervals.[2] To quantify the change from preoperative test to the postoperative tests scores, separate and composite z-scores will be calculated on the basis of the seven cognitive test results and compared using Mann-Whitney U rank sum test.

To analyse differences in biomarkers within patients and between patients, χ^2 or Student's t-test will be used. To analyse differences within patients and between patients in cognitive performance and postoperative recovery, Mann-Whitney U rank sum tests will be used. For statistical analyses, IBM SPSS statistics V.24 for Windows will be used (IBM, Armonk, New York, USA). A p value of <0.05 will be considered to be statistically significant in all analyses.

Descriptive statistics of demographic and perioperative data will be presented by number, percentage and mean (SD) or min-max, as appropriate. Depending on the results from the cognitive tests and biomarkers, the patients will be stratified on the basis of their postoperative composite cognitive z-score result into two groups: no delayed neurocognitive recovery corresponding to a composite z-score <1 or delayed neurocognitive recovery with composite z-score ≥1.0.[2] Patient characteristics will be compared, between these two groups, using Fisher's exact test for categorical outcomes and t-tests or the Wilcoxon rank-sum test for continuous variables, as appropriate. A difference will be considered if any of these characteristics between the two groups has a p value of <0.05.

The analytical point of integration

The qualitative and quantitative findings will be brought together to look for similarities, that is, whether the qualitative and the quantitative findings yield convergent results (*triangulation*)[22] or if they are diverged. Thereafter, the findings from the interviews, both patients and relatives, will be sorted out depending on group stratification (no delayed neurocognitive recovery or delayed neurocognitive recovery). The qualitative and quantitative findings will then be compared to seek for similarities and differences. All patients will be included in the mixed data analysis even though they have an improvement in z-score, SwQoR or biomarkers.

Dissemination

The study results will be disseminated through peer-reviewed publications and conference presentations to the scientific community and social media.

Patient and public involvement

Patients were not involved in the design of the study and will not be involved in the recruitment of participants. The results of the project will be disseminated through scientific papers.

DISCUSSION

Knowledge can be obtained both by understanding and explaining a phenomenon of interest, which is the reason why a mixed-methods design including both qualitative and quantitative data will be used. By merging qualitative and quantitative data, we will look for confirmation, expansion and discordance in the different datasets. Confirmation occurs when the data confirm each other, that is, that the results from the qualitative and quantitative analyses confirm the results in the respective outcome. The data can also expand, that is, when the outcomes diverge and expand or complement the results from the qualitative and quantitative findings. Discordance occurs when the results from the different data conflict, or disagree, with each other.[21 22] When results from the quantitative and qualitative study do not match completely, this enhances the robustness of the study by illustrating the complexity of the problem studied.[28] In this study, the quantitative data include both objective (biomarkers and cognitive testing) and subjective (SwQoR and postoperative pain) outcomes and the qualitative data include both the patient's and the relative's view.

POCD is a major neurological adverse outcome following major surgery[5 6 29] with age as one of the major risk factors.[2 4] Cognitive assessment in order to capture POCD is not a routine part of clinical practice, and nor do we have any evidence for patients' and their relatives' own experience of suffering from POCD and whether there is a relation between objective and subjective outcomes of it. The knowledge from the present project as well as earlier evidence from studies assessing POCD will create a base in developing a gamified version of the traditional pen-and-paper cognitive assessment tools, in order to start assessing POCD in an easy and secure way in clinical practice. Until this is done, the results from the present project will generate evidence for clinical practice to detect patients with POCD by identifying signs and symptoms that patients and their relatives themselves describe when suffering from POCD.

ETHICAL CONSIDERATIONS

It is recognised that the study protocol involves cognitive tests that may display pre-existing and previously unknown cognitive impairment.[30] Detailed information about the extent and duration of cognitive tests, including possible outcomes, will be carefully explained and the patient and the relative can refuse to participate on the basis of this information. In addition, participants will be informed that the study is voluntary and that the data would be treated with confidentiality. They will also be informed that they can terminate their participation at any time. Written informed consent will be obtained from the participants after they have received written and verbal information about the study, including the purpose and procedures, the voluntariness of participation and the option to withdraw at any time. They will also be guaranteed confidentiality and secure data storage. We will follow good clinical practice in the conduct of clinical trials.

The study follows the recommendations of the World Medical Association General Assembly that include principles considering the prospective registration and the public disclosure of study results to be ethical obligations, as follows: '*Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject'* and '*Negative and inconclusive as well as positive results should be published or otherwise made publicly available'*. All researchers will follow the Uniform Requirements for Manuscripts.[31]

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Patient consent for publication Not required.

Ethics approval The project has been approved by the Swedish Ethical Review Authority (2019–02968) and will follow the principles outlined in the 1964 Helsinki Declaration and its later amendments.

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