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Cognitive Dysfunction After Fast-Track Hip and Knee Replacement

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BACKGROUND: Postoperative cognitive dysfunction (POCD) is reported to occur after major surgery in as many as 20% of patients, elderly patients may especially experience problems in the weeks and months after surgery. Recent studies vary greatly in methods of evaluation and diagnosis of POCD, and the pathogenic mechanisms are still unclear. We evaluated a large uniform cohort of elderly patients in a standardized approach, after major joint replacement surgery (total hip and knee replacement). Patients were in an optimized perioperative approach (fast track) with multimodal opioid-sparing analgesia, early mobilization, and short length of stay (LOS ≤3 days) and discharged to home.

METHODS: In a prospective multicenter study, we included 225 patients aged ≥60 years undergoing well-defined fast-track total hip or total knee replacement. Patients had neuropsychological testing preoperatively and 1 to 2 weeks and 3 months postoperatively. LOS, pain, opioid use, inflammatory response, and sleep quality were recorded. The practice effect of repeated cognitive testing was gauged using data from a healthy community-dwelling control group (n = 161).

RESULTS: Median LOS was 2 days (interquartile range 2–3). The incidence of POCD at 1 to 2 weeks was 9.1% (95% confidence interval [CI], 5.4%–13.1%) and 8.0% (95% CI, 4.5%–12.0%) at 3 months. There was no statistically significant difference between patients with and without early POCD, regarding pain, opioid use, sleep quality, or C-reactive protein response, although the CIs were wide. Patients with early POCD had a higher Mini Mental State Examination score preoperatively (difference in medians 0.5 [95% CI, −1.0% to 0.0%]; P = 0.034). If there was an association between early POCD and late POCD, the sample size was unfortunately too small to verify this (23.6% of patients with early POCD had late onset vs 6.7% in non-POCD group; risk difference 16.9 (95% CI, −2.1% to 41.1%; P = 0.089).

CONCLUSIONS: The incidence of POCD early after total hip and knee replacement seems to be lower after a fast-track approach than rates previously reported for these procedures, but late POCD occurred with an incidence similar to that in previous studies of major noncardiac elective surgery. No association between early and late POCD could be verified. (Anesth Analg 2014;118:1034–40)

Cognitive changes after major surgery have received increased attention in the literature in recent years.[1–6] The surgical population is aging due to an increased elderly population, as well as advances in anesthesia and surgical techniques, and the impact of postoperative cognitive complications will take up increasing resources in years to come. Cognitive dysfunction is reported to play a significant role in prolonged recovery after major surgery in elderly patients.[5]

Postoperative cognitive problems are within different categories, and diagnosis and classification are not uniform among studies.[7,8] Postoperative cognitive dysfunction (POCD) is diagnosed using cognitive test scores to detect changes developing postoperatively, compared with each individual patient's preoperative cognitive level of functioning. POCD affects a wide range of cognitive domains, such as memory, attention, orientation, and concentration, and some patients experience difficulties for months postoperatively.[9] POCD has been described after both cardiac and noncardiac surgery and can occur in all age groups, although the elderly are more at risk.[6–8,10]

The pathogenic mechanisms behind the development of POCD are unclear, partly due to the variation in patient population, diagnostic tools, and analysis of cognitive test results in the literature, making firm conclusions on the pathogenic mechanisms difficult.[7] However, most agree that increasing age, reduced preoperative cognitive reserve, and low educational level are risk factors for POCD.[7,8,11,12] A distinction between acute and elective surgery, as well as cardiac versus noncardiac surgery, is necessary when evaluating cognitive changes.

Postoperative care is undergoing major advances within the health care system, and the postoperative recovery period is forever shortening, especially duration of hospital stay, which has markedly decreased within the past decade.[13,14] Previous studies of POCD after major surgery

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have focused on traditional perioperative care with a relatively long length of stay (LOS). We have previously hypothesized that an optimized perioperative approach with short LOS, multimodal opioid-sparing analgesia, early mobilization, and discharge to home environment (the fast-track approach) would impact the occurrence of cognitive changes after major surgery.[7]

The aim of this study was to evaluate the incidence of POCD after major joint replacement surgery in patients aged ≥60 years early after surgery (1–2 weeks postoperatively). Fast-track total hip or knee arthroplasty (THA/TKA) in a standardized perioperative approach was used as a model for major elective noncardiac surgery in general, since this would enable us to test a large cohort of relatively uniform patients undergoing a standardized surgical procedure receiving similar perioperative care. The secondary aims of the study were to evaluate a possible association between POCD and postoperative pain, opioid use, subjective postoperative sleep, and the inflammatory response (C-reactive protein [CRP]). We also evaluated POCD at 3 months to gather information on the possible predisposition of late-onset POCD if early POCD was present.

METHODS

Patients were included in a prospective multicenter study of POCD after fast-track THA and TKA. The study was approved by the Regional Ethics Committee (Reg. No. H-3-2009-096), and patients gave written informed consent before participation. The study was registered at ClinicalTrials.gov (ID No. NCT01103752).

The inclusion period began on February 15, 2010, and was concluded on December 8, 2011. Eligible patients were having elective THA and TKA in a fast-track approach at 4 hospitals (Gentofte, Hørsholm, Holstebro, and Århus). All participating departments had a fully implemented fast-track regime with anticipated LOS of ≤3 days.[13,15]

The fast-track approach is a standardized regime beginning before surgery where all patients are thoroughly informed of the surgical procedure, anesthesia, and analgesia perioperatively. Furthermore, physiotherapists instruct all patients in the use of crutches and relevant exercises pre- and postoperatively. The patients' own role and responsibility in their own rehabilitation was stressed when receiving this information, as well as the anticipated short LOS with discharge to home. All participating hospitals had a very similar routine within the fast-track approach. Surgery was performed by experienced arthroplasty surgeons at the consultant level with only small variations in surgical technique among surgeons, and all used a minimally invasive procedure with similar duration of the surgical procedures (Table 2). The technique is described by Husted et al.[15] The hospitals differed slightly in analgesic approach as is thoroughly described elsewhere.[16]

Patients had to be ≥60 years of age and ASA physical health class I to IV. Exclusion criteria were anesthesia within the past 30 days, dementia (defined by Mini Mental State Examination [MMSE] score ≤2), or Parkinson or other neurological disease causing functional impairment. Patients with a history of alcohol abuse (≥35 U per week) or daily use of anxiolytics were also excluded, as well as those with severe hearing or visual impairment. All patients had to be fluent in written and spoken Danish and be able to cooperate with neuropsychological testing.

The postoperative analgesic regime was standardized according to hospital guidelines. All patients received paracetamol and nonsteroidal anti-inflammatory drugs, and 2 centers also gave gabapentin twice daily. Opioids were given on request as rescue analgesia postoperatively (tramadol, oxycodone, or morphine).[16] Patients did not receive any sedative premedication (no benzodiazepines or hypnotics), and spinal anesthesia without opioid was the standard. Propofol was given if sedation was needed during surgery, and level of sedation was adjusted, so patients were relaxed and drowsy but with a purposeful response to verbal stimulation. General anesthesia was used only if spinal anesthesia was unsuccessful or contraindicated. During anesthesia, arterial blood pressure was monitored noninvasively and measured every 2 to 5 minutes. Ephedrine 5 to 10 mg or phenylephrine 0.1 mg was given if mean arterial blood pressure decreased <25% of baseline, and systolic blood pressure was kept >80 to 90 mm Hg.

All patients received standardized postoperative care and were discharged to home, when they fulfilled well-defined discharge criteria.[15] Postoperative mobilization was started on the day of surgery with support from nursing staff, and physiotherapy was started the following day. Patients were encouraged to ambulate freely and exercise according to the instructions given preoperatively.

All patients had neuropsychological testing once preoperatively and 1 to 2 weeks and 3 months postoperatively. The neuropsychological test battery consisted of 4 different tests focusing on different cognitive domains susceptible to dysfunction after surgery. The neuropsychological test battery consisted of the following tests and is described in detail elsewhere.[17]

- Visual Verbal Learning Test (VVLT)
- Concept Shifting Test
- Stroop Color Word Test
- Letter Digit Coding Task.

To evaluate possible cognitive dysfunction, 7 variables were analyzed using z scores. The 7 variables were total number of words recalled in 3 trials of VVLT, number of words recalled in the delayed part of VVLT, time and number of errors in Concept Shifting Test part C, time and number of errors in Stroop Color Word Test part 3, and total number of correct items in the Letter Digit Coding Task.[8]

Since these tests are prone to test–retest practice effect, a healthy age-matched control group (n = 161) was tested at the same intervals and provided an indication of practice effect with this test battery for the given time intervals between sessions. The results from the healthy control group are described in detail elsewhere.[17]

The tests were administered in the same sequence at each test session by a trained research nurse following a standardized instruction manual to ensure as uniform a test situation as possible. Research nurses had frequent audit by the primary investigator (LK), and all sessions were administered by the same nurse, whenever possible.

POCD was defined as 2 individual z scores >1.96 or a composite z score >1.96. Data from the healthy control

group were used to gain information on practice effect and normal distribution in test results for this age group, and z scores were calculated. These diagnostic criteria are in line with the recommendations from the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group.[8]

Besides the neuropsychological tests, patients were asked to complete a questionnaire preoperatively about their comorbidities, daily use of medication, educational status, and sleep pattern with the Pittsburg Sleep Questionnaire Index.[18] All patients were screened for sleep apnea and dementia preoperatively with the Berlin Questionnaire and MMSE.[19,20] Information about anesthetic technique and duration, procedure duration, use of analgesics, use of hypnotics during hospitalization, postoperative complications, and LOS were recorded. Pain at rest and while walking were assessed using a numerical ranking scale of 0 to 10 (0 = "no pain" and 10 = "the most excruciating pain imaginable") before each test session. To assess inflammation, CRP blood concentration was analyzed at the preoperative test session, on postoperative day 1 or 2 and on the first postoperative test session (1–2 weeks postoperatively).

Data on clinically overt postoperative delirium in this group have been reported previously.[16]

Statistics

The z scores were calculated as described in detail elsewhere.[8] Continuous data are reported in the tables as median and interquartile range (IQR) and categorical data as frequency (*n*) and percentage, stratified by early POCD. The association between continuously valued variables and POCD was assessed by the difference in medians of patients with or without POCD. The association between categorical variables and POCD was assessed by the difference in risk for POCD between the category and the baseline category in percent points, including the association between early- and late-onset POCD. A 95% confidence interval (CI) and corresponding *P* value were calculated for the above difference estimates with a nonparametric bootstrap using 10,000 replications, this is also the case for the 95% CI for incidence estimates.[21]

Sample size was calculated to obtain a power of 0.85 at a significance level of 0.05. We sought to obtain sufficient data on early POCD (at 1–2 weeks) to discern a reduction from the previously reported 20% POCD incidence among the elderly undergoing major surgery (from the ISPOCD group) to an anticipated level of about 10% which required evaluation of 220 patients.

RESULTS

We approached 311 patients for participation in the study. Eighty-four patients declined to participate, and 2 patients were excluded due to MMSE score <24. The remaining 225 patients were included. Five patients (2%) failed to show up for their first postoperative evaluation, and 25 failed to show up for their final evaluation at 3 months (drop-out rate 11.2% for final visit). Hence, the remaining 220 patients' cognitive test results were included in the diagnosis of early POCD (at 1–2 weeks) and from 200 patients at 3 months.

The median age was 68 years (IQR 64–73 years). Eighty-one patients had TKA and 144 had THA. The median MMSE score was 28 (IQR 24–30), and mean LOS was 2 days (IQR 2–3). Spinal anesthesia was performed in 203 patients (90.2%), and 49.7% of these received supplemental propofol sedation. The remaining 22 (9.9%) patients received general anesthesia. Comorbidity, perioperative data, complications, and readmission are shown in Tables 1 to 3.

Table 1. Comorbidity for Patients Undergoing Hip or Knee Arthroplasty

Comorbidity	No. of patients
Hypertension	126
Heart disease (AF, heart failure, valve disease)	28
Lung disease (asthma, COPD)	15
Diabetes—IDDM/NIDDM	1/17
Psychiatric illness	17
Prior stroke	12
Sleep apnea	7

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; IDDM/NIDDM = insulin/noninsulin-dependent diabetes.

Table 2. Perioperative Data Stratified on the Presence of Early Postoperative Cognitive Dysfunction

Perioperative data	Early POCD	Not early POCD	Difference[a]	*P* value
ASA class, *n* (%)				
I	6 (8.7)	63 (91.3)	0	
II	10 (7.2)	129 (92.8)	−1.5 (−9.8 to 6.3)	0.74
III	4 (33.3)	8 (66.7)	24.6 (−2.3 to 56.9)	0.071
IV	0	0	—	—
Procedure, *n* (%)				
Hip arthroplasty	11 (7.7)	131 (92.3)	0	
Knee arthroplasty	9 (11.5)	69 (88.5)	3.8 (−4.5 to 12.5)	0.40
Duration of anesthesia (min), median (IQR)	120 (95 to 135)	115 (100 to 135)	−5 (−25 to 20)	0.44
Duration of surgery (min), median (IQR)	63 (45 to 75)	55 (45 to 70)	−8 (−20 to 10)	0.44
Anesthesia method, *n* (%)				
Neuraxial block	18 (9.1)	180 (90.9)	0	
General	2 (9.1)	20 (90.9)	0 (−11.1 to 14.9)	0.96
Intraoperative sedation, *n* (%)				
No	9 (7.8)	107 (92.2)	0	
Yes	11 (10.6)	93 (89.4)	2.8 (−4.8 to 10.5)	0.47
Length of stay (d), median (IQR)	2.5 (2.0 to 3.0)	2.0 (2.0 to 3.0)	−0.5 (−1.0 to 1.0)	0.39

POCD = postoperative cognitive dysfunction; IQR = interquartile range.

[a]Difference in risk for early POCD between the corresponding category and the baseline (first) category in percent points and 95% confidence interval (categorical variables), or difference in medians between early POCD and not early POCD and 95% confidence interval (continuous variables).

Median time from preoperative test to surgery was 6 days (5%–95% range 2–14 days). The test was performed within regular daytime hours (8:00 AM–4:00 PM). The first postoperative test was performed after a median of 12.0 days (IQR 11–13 days) postoperatively and the second test after a median of 14 weeks (IQR 13–16 weeks) postoperatively. The incidence of early POCD (POCD criteria fulfilled at the first test session) was 20 per 220 (9.1%; 95% CI, 5.4%–13.1%).

Table 3. Postoperative Complications Evaluated at Test Session 1 and 2

Postoperative complication	No. of patients	Time after surgery
Pneumonia	1	Within 1 wk
Pulmonary embolism	2	Within 3 mo
Deep venous thrombosis	0	—
Myocardial infarction	0	—
Stroke	0	—
Stay in intensive care unit	0	—
Wound infection	5	Within 1 wk
Dislocation	3	Within 3 mo[a]
Sepsis	0	—
Gastric ulcer	4	2 within 1 wk, 2 within 3 mo
Blood transfusion	1[b]	—
Other	2	Within 1 wk

[a]The 3 dislocations all resulted in readmission for closed repositioning.
[b]Blood transfusion due to peptic ulcer 3 days after surgery.

The incidence of late POCD (criteria fulfilled at the 3-month test session) was 16 per 199 (8.0%; 95% CI, 4.5%–12.0%). No statistically significant differences in CRP, pain, sleep quality, or opioid use were found in relation to early POCD, but CIs were wide (Table 4).

We sought to evaluate whether there was an association between early and late POCD (23.6% late POCD in the group of patients with early POCD vs 6.7% in the group without, risk difference 16.9 [95% CI, −2.1% to 41.1%; $P = 0.089$]), but the wide CI cannot support this assumption. Patients with early POCD may have had a higher MMSE score than patients without (difference in medians −0.5 [95% CI, −1.0% to 0.0%; $P = 0.034$]). There was no evidence of differences between groups regarding gender, age, or educational level (Table 5).

DISCUSSION

In this study, we evaluated the incidence of POCD after fast-track THA and TKA in an elderly population (aged ≥60 years), using a well-recognized cognitive test battery, and data from an age-matched healthy control group to gauge the level of practice effect with repeated testing. Compared with previous results, our results showed a low incidence of POCD early after surgery, 9.1% (at 1–2 weeks) but a similar incidence of 8.0% at 3 months postoperatively. We did not find a clear difference between early POCD patients and patients without early-onset POCD regarding the proposed

Table 4. Data Regarding Inflammation C-Reactive Protein, Sleep Quality (Pittsburg Sleep Questionnaire Index), Pain, and Opioid Use

Variable	Early POCD	Not early POCD	Difference[a]	*P* value
CRP at preoperative test (mmol/L)	2.0 (1.0 to 7.5)	2.0 (1.0 to 4.0)	0.0 (−2.5 to 1.0)	0.84
CRP at postoperative day 1 (mmol/L)	54.0 (20.0 to 70.0)	64.0 (46.0 to 80.0)	10.0 (−6.5 to 30.5)	0.38
CRP at postoperative day 2 (mmol/L)	194.5 (77.0 to 280.0)	142.0 (51.0 to 206.0)	−52.5 (−148.5 to 63.0)	0.26
CRP at 1st postoperative test (mmol/L)	15.0 (7.0 to 25.0)	15.0 (8.0 to 21.0)	0.0 (−11.0 to 8.0)	0.69
PSQI at preoperative test	6.0 (3.0 to 8.5)	6.0 (3.0 to 9.0)	0.0 (−3.0 to 2.0)	0.55
PSQI at 1st postoperative test	9.5 (3.5 to 11.0)	7.0 (4.0 to 10.0)	−2.5 (−4.0 to 3.0)	0.26
Pain score at preoperative test—at rest	2.0 (0.0 to 5.0)	2.0 (0.5 to 3.0)	0.0 (−2.0 to 2.0)	0.99
Pain score at preoperative test—activity	5.0 (3.5 to 8.0)	5.0 (4.0 to 6.5)	0.0 (−2.5 to 1.5)	0.68
Pain score at 1st postoperative test—at rest	2.5 (0.0 to 5.0)	2.0 (0.5 to 3.0)	−0.5 (−2.5 to 1.0)	0.55
Pain score at 1st postoperative test—activity	3.5 (1.5 to 5.5)	3.5 (2.0 to 4.5)	0.0 (−2.0 to 2.0)	0.67
Opioid use[b] in hospital (mg/d)	31.7 (15.0 to 40.0)	22.5 (10.0 to 35.0)	−9.2 (−20.0 to 6.7)	0.33
Opioid use[b] in hospital (mg/d/kg)	0.33 (0.17 to 0.48)	0.29 (0.14 to 0.45)	−0.04 (−0.19 to 0.11)	0.48

Median values (interquartile range), stratified on early POCD.
CRP = C-reactive protein; PSQI = Pittsburg Sleep Questionnaire Index; POCD = postoperative cognitive dysfunction.
[a]Difference in medians between early POCD and not early POCD and 95% confidence interval.
[b]Opioid dosage has been calculated in equipotent morphine dosage where medication other than oral morphine was administered.

Table 5. Preoperative Patient-Specific Nonmodifiable Characteristics

Preoperative patient characteristics	Early POCD	Not early POCD	Difference[a]	*P* value
Age (y), median (IQR)	72.0 (66.0 to 76.0)	68.0 (64.0 to 73.0)	−4.0 (−7.5 to 2.0)	0.15
Gender, *n* (%)				
Male	10 (9.3)	98 (90.7)	0	
Female	10 (8.9)	102 (91.1)	−0.3 (−7.9 to 7.3)	0.94
MMSE score, median (IQR)	29.5 (28.5 to 30.0)	29.0 (28.0 to 30.0)	−0.5 (−1.0 to 0.0)	0.034
Educational level,[b] *n* (%)				
Low	10 (11.9)	74 (88.1)	0	
Medium	4 (15.4)	22 (84.6)	3.5 (−11.2 to 20.3)	0.69
High	5 (4.7)	102 (95.3)	−7.2 (−15.4 to 0.7)	0.079

MMSE= Mini Mental State Examination; POCD = postoperative cognitive dysfunction; IQR = interquartile range.
[a]Difference in risk for early POCD between the corresponding category and the baseline (first) category in percent points and 95% confidence interval (categorical variables), or difference in medians between early POCD and not early POCD and 95% confidence interval (continuous variables).
[b]Educational level is divided into 3 groups according to the educational system in Denmark: low (<13 years), medium (13–15 years), high (>15 years).

risk factors (inflammation, pain, disturbed sleep, opioid use). However, early POCD did not clearly predispose to late-onset POCD. We observed very few postoperative complications, and an analysis of a possible association between early- or late-onset POCD with postoperative complications was not meaningful.

Our data suggest a lower incidence of early-onset POCD than previously reported.[22–26] The largest trial to evaluate POCD in noncardiac surgery is still the ISPOCD study from 1998 in which early POCD was seen in 26% of patients 1 week postoperatively.[23] The ISPOCD study included numerous patients undergoing hip and knee replacement, and at 1 week, POCD was found in 57 of the 303 orthopedic patients tested (18.9%) and in 10.8% (31 of 287) at 3 months. More recent studies have reported incidences of 20% to 40% when testing at 1 week after surgery.[22,24–26] Despite the differences in methods, our results are significantly lower than this. Unfortunately, it is very difficult to compare these findings in an optimal way, as details related to the perioperative care have not routinely been reported.[22] As we have previously hypothesized, we believe these factors play a significant role in the development of cognitive decline, and it is most unfortunate that such basic perioperative data are lacking in otherwise well-conducted studies, which makes direct comparison problematic.[5,7] It seems that the fast-track approach had an impact on the patients' cognition early on, but is less important for late-onset POCD. Which factors play a role for later development of cognitive dysfunction after surgery are unclear and are probably also harder to assess than early POCD, since several other factors may influence POCD during the longer time interval.

The average duration of surgery was about an hour, with very little variation, which is probably a result of the surgeons' high level of experience and the standardization of the approach. THA was performed using the posterior approach and mainly uncemented, with incisions <15 cm. TKA was performed using an anterior midline approach in all cases. Incision length was 10 to 15 cm, and cemented and uncemented implants were used. Duration of surgery is well below that of previously reported studies[27] and reflects the fact that only consultant-level surgeons performed the operations, resulting in a low level of blood loss and postoperative complications. This, combined with the other optimized perioperative factors (analgesic regime, intense ambulation, and short LOS) may very well have been a factor in the low incidence of early POCD.

Our results showed a tendency for a higher preoperative MMSE score in the group who developed early POCD (P = 0.06) which is in contrast to earlier studies showing a low preoperative cognitive reserve to predispose to POCD.[9,24] In line with previous studies that found increasing age to predispose to cognitive changes after major surgery, our results also showed a tendency for increasing age to be a risk factor for early POCD, while not statistically significant, the wide 95% CI does not exclude the presence of a difference between groups. This increased sensitivity to cognitive changes with increasing age may have been due to a wide spectrum of factors. Changes in environment and disturbances in daily rhythm have been shown to have a greater impact on the elderly. Furthermore, the intrinsic factors of the immediate postoperative recovery period with decreased function, postoperative pain, and opioid administration, all affect elderly patients more than their younger counterparts.

The fast-track approach uses a multimodal pain management regime to reduce the use of opioids and pain levels. This study did not analyze pain scores immediately after surgery, but other studies, with the same approach and similar patient group, have reported only moderate pain during ambulation in the first 48 hours postoperatively,[28] in accordance with our findings (Table 4). Postoperative pain levels do not only affect opioid administration, but also have an impact on rehabilitation and sleep.[29,30] Sleep, pain, opioids, and inflammation are part of an intricate circle of interactions, where sleep disruptions may cause hyperalgesia which increases demand for opioids and opioids in themselves disrupt sleep.[31,32] Several studies have illustrated a connection between sleep and cognitive abilities, where the elderly experienced prolonged cognitive effects due to sleep deprivation.[33,34] Sleep architecture and duration are negatively affected by pain, opioids, and inflammation, all factors that play a role in the immediate recovery period.

We only evaluated sleep subjectively with a questionnaire that may not have been the most reliable way to assess sleep architecture and quality, since there tend to be discrepancies between objective and subjective sleep data. However, obtaining objective sleep data from >200 patients with electroencephalography over a sustained period of time is not feasible. Nevertheless, our more specific electroencephalography and actigraphy studies, in smaller groups of fast-track TKA and THA patients, have shown a significant disturbance in sleep architecture immediately after surgery,[35,36] with rapid eye movement sleep being almost absent on the first postoperative night but normalized about 2 days after discharge. This may be relevant since a normal sleep pattern is important for intact cognitive abilities, and even a short period of disturbed sleep pattern and lack of rapid eye movement sleep during the first or second postoperative night may contribute to early postoperative cognitive decline.

A limitation of our study is that the contribution of each element in the fast-track approach cannot be analyzed in detail. However, this study is the first to comprehensively report on such a uniform cohort of elderly patients and render new knowledge on early-onset POCD after major surgery in a standardized approach. The results of an enhanced recovery in early cognitive dysfunction is in accordance with other functional improvements in the fast-track approach.[37] The data analysis included a consideration of the practice effect, based on data from the large community-dwelling age-matched control group. Optimally, the control group needs to be matched to the patient cohort as much as possible, regarding age, comorbidity, cognitive reserve, etc. The fact that our control group was community-dwelling healthy elderly people may have affected their cognitive performance, and they may have performed better than our patient group. However, the aim of the cognitive testing of the controls was not to gather data on their absolute cognitive performance but to gather information on the practice effect with repeated cognitive testing. As such, we believe that the data collected from our healthy control give

a very good indication of the practice effect within this age group. Furthermore, a main strength of our study was each center's strict adherence to protocol on testing intervals and follow-up, resulting in low dropout rates. However, the patients who dropped out of the study for the final visit (11%) may have contributed to a higher incidence of late-onset POCD, and the incidence of 8% may in reality be higher, since patients who believe they may have memory deficits postoperatively may be more likely to drop out. The dropout rate in our study is low compared with other studies, but this uncertainty as to the memory status of the final 11% of patients is a weakness. However, 3-month follow-up was not our primary end point.

Future optimization of cognitive function postoperatively in the elderly after major surgery needs to focus on a multifactorial approach. Increasing age, preoperative educational level, and cognitive reserve are nonmodifiable factors since they characterize the individual patient.[38] Current efforts to modify cognitive reserve and delay or prevent cognitive decline in the individual are receiving a lot of attention, and in the future, there may be some way to implement these efforts to prevent postoperative decline. However, at the current stage, these efforts are more focused on the long-term decline due to increased longevity in the population, and we do not believe preoperative optimization of cognitive reserve plays an important role in POCD. There are modifiable factors in the perioperative care that may contribute to a better prognosis for cognition after major surgery.[38] Thus, a joined effort of multimodal opioid-sparing analgesia, together with a reduction of the inflammatory response with preoperative steroids, may potentially further reduce the undesirable effects on cognition.[28,37,39] In addition, the effect of a short-acting hypnotic for the first 2 postoperative nights to alleviate sleep deprivation needs to be studied.

In conclusion, our data suggest that the incidence of POCD early after THA and TKA is lower after a fast-track approach, but late POCD occurred at a similar rate as previously reported results after major noncardiac elective surgery. The mechanisms behind this reduction are probably multifactorial with nonmodifiable factors (age, educational level, cognitive reserve) and potentially modifiable factors (pain, inflammation, opioid use, and sleep disturbances).

DISCLOSURES

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Attestation: Lene Krenk has approved the final manuscript and has also reviewed the original data and data analysis. Lene Krenk is also the archival author.
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