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Postoperative cognitive changes after total knee arthroplasty under regional anesthesia

Young-Tae Jeon, MD, PhD[a], Byung-Gun Kim, MD[b], Young Ho Park, MD[c,d], Hye-Min Sohn, MD[a], Jungeun Kim, MD, PhD[c,d], Seung Chan Kim, MS[e], Seong Soo An, PhD[e], SangYun Kim, MD, PhD[c,d,*]

Abstract

Background: The type of postoperative cognitive decline after surgery under spinal anesthesia is unknown. We investigated the type of postoperative cognitive decline after total knee arthroplasty (TKA). Neuropsychological testing was conducted and the changes in cerebrospinal fluid (CSF) biomarkers after surgery were evaluated.

Methods: Fifteen patients who required bilateral TKA at a 1-week interval under spinal anesthesia were included. Neuropsychological tests were performed twice, once the day before the first operation and just before the second operation (usually 1 week after the first test) to determine cognitive decline. Validated neuropsychological tests were used to examine 4 types of cognitive decline: memory, frontal-executive, language-semantic, and others. Concentrations of CSF amyloid peptide, tau protein, and S100B were measured twice during spinal anesthesia at a 1-week interval. The patients showed poor performance in frontal-executive function (forward digit span, semantic fluency, letter-phonemic fluency, and Stroop color reading) at the second compared to the first neuropsychological assessment.

Results: S100B concentration decreased significantly 1 week after the operation compared to the basal value (638 ± 178 vs 509 ± 167 pg/mL) ($P = 0.019$). Amyloid protein $\beta 1-42$, total tau, and phosphorylated tau concentrations tended to decrease but the changes were not significant.

Conclusion: Our results suggest that frontal-executive function declined 1 week after TKA under spinal anesthesia. The CSF biomarker analysis indicated that TKA under regional anesthesia might not cause neuronal damage.

Abbreviations: Aβ = amyloid beta protein, AD = Alzheimer's disease, BNT = Boston naming test, CSF = cerebrospinal fluid, MMSE = Mental State Examination, POCD = postoperative cognitive dysfunction, RCFT = Rey–Osterrieth Complex Figure Test, SVLT = Seoul Verbal Learning Test, TKA = total knee arthroplasty.

Keywords: cerebrospinal fluid biomarkers, postoperative cognitive changes, reginal anesthesia, total knee arthroplasty

[a] Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, [b] Department of Anesthesiology and Pain Medicine, Inha University School of Medicine, Inha University Hospital, [c] Department of Neurology, Seoul National University College of Medicine, Seoul, [d] Clinical Neuroscience Center, Seoul National University Bundang Hospital, Seongnam, [e] College of BioNano technology, Gacheon University, South Korea.

* Correspondence: SangYun Kim, Clinical Neuroscience Center, Seoul National University Bundang Hospital, Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea (e-mail: mirrorcastle@daum.net).

1. Introduction

Postoperative cognitive dysfunction (POCD) can occur after surgery. POCD occurs in 25.8% of elderly patients (>60 years) within 1 week after surgery and in 9.9% of patients between 1 week and 3 months after surgery.[1] Although various factors including the types of anesthesia and surgery, comorbidities, and perioperative conditions are alleged to contribute to POCD[2,3], the exact etiology remains obscure. Neuropsychological testing has been performed to investigate the occurrence of POCD. The type of cognitive impairment has been examined to determine which brain systems are vulnerable to perioperative events.[4] Memory and executive function have been assessed. Identifying the type of cognitive decline may help elucidate the mechanism of POCD. We hypothesized that more comprehensive neuropsychological testing may be required for this purpose.

The role of Alzheimer's disease (AD) biomarkers, such as amyloid beta protein (Aβ)1–42, total tau, and P-tau181P, in POCD was identified by a study of changes in cerebrospinal fluid (CSF) biomarker levels after cardiac surgery.[5] The incidence of AD increases markedly after cardiac surgery.[6,7] Cognitive impairment after coronary artery bypass graft surgery is associated with changes in AD biomarker levels and S100B.[5] However, no study has examined the changes in biomarkers after noncardiac surgery under regional anesthesia.

We investigated the mechanism underlying POCD by examining the type of POCD and analyzed changes in cerebrospinal fluid (CSF) biomarkers after total knee arthroplasty

(TKA). We performed comprehensive neuropsychological testing and analyzed AD biomarker levels and S100B.

2. Materials and methods

2.1. Patients

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital, and informed consent was obtained from all patients. This trial was registered at Korean Clinical Trials Registry (http://cris.nih.go.kr, number KCT0001044). Patients aged < 85 years (American Society of Anesthesiologists physical status I-II) who required bilateral TKA at a 1-week interval under spinal anesthesia were included. Patients with a contraindication to spinal anesthesia or a history of psychiatric or neurologic diseases were excluded. Furthermore, patients who refused to participate or who were unable to pass the neuropsychological tests were excluded. Sixteen patients were enrolled. One patient declined to participate after the first neuropsychological test; thus, 15 patients were included in the final analysis.

2.2. Neuropsychological tests

All patients underwent a detailed neuropsychological battery twice; once on the day before the first operation and 1 week after the first test (1 day before the second operation). The battery of tests assessed attention, language, visuospatial ability, verbal and visual memory, and frontal/executive function and comprised the following tests: digit span (forward and backward), the Korean version of the Boston Naming Test (BNT), the Rey–Osterrieth Complex Figure Test (RCFT) (copying, immediate, and 20-min delayed recall and recognition), the Seoul Verbal Learning Test (SVLT) (3 learning-immediate recall trials of a 12 item list, a 20-min delayed recall trial for the 12 items and recognition testing), and a test of semantic fluency (animal) and letter-phonemic fluency (the Controlled Oral Word Association Test). The Stroop test (correct number of responses for word reading and naming the color of the font for 112 items during a 2-min period) was also used.

A factor analysis revealed 4 types of cognitive function. These were: Factor 1 (memory domain): RCFT, SVLT, time orientation; Factor 2 (frontal-executive domain): digit span forward/backward, letter-phonemic word fluency, Stroop color reading; Factor 3 (language-semantic domain): animal/supermarket word fluency, SVLT, BNT; and Factor 4 (others): RCFT copy and Stroop word reading.

2.3. Anesthesia and surgery

A femoral nerve block and spinal anesthesia were performed by 1 experienced anesthesiologist, and included electrocardiography as well as noninvasive blood pressure and pulse oximetry monitoring. A femoral nerve catheter was placed between the fascia iliaca anterior to the femoral nerve for postoperative pain control using ultrasonography. Spinal anesthesia was performed with 10 to 12 mg 0.5% heavy bupivacaine at the L3–4 intervertebral space with the patient in the lateral decubitus position. Before administration of heavy Marcaine, CSF was collected in a sample tube for biomarker assays. After removing 1 mL of CSF, 5 mL of CSF were collected in a bottle. The CSF was transferred immediately on ice and stored at $-70°C$ for later assay.

All surgeries were performed by 1 experienced surgeon using the standard medial parapatellar arthrotomy with a tourniquet. A posterior-stabilized prosthesis (Genesis II, Smith & Nephew,

Memphis, TN) was implanted during all TKAs. In all cases, the patella was resurfaced, and the implant was fixed with bone cement.

A multimodal analgesic regimen was used for postoperative pain control after TKA. This therapy comprised preemptive analgesia, periarticular injection during the operation, continuous femoral nerve blockade, intravenous patient-controlled analgesia, and postoperative oral analgesics. Preemptive analgesia included 200-mg celecoxib, 10-mg sustained-release oxycodone, 10-mg oxycodone, 75-mg pregabalin, and 650-mg acetaminophen. The periarticular injectate comprised 10-mg morphine sulfate, 300-mg ropivacaine, 30-mg ketorolac, 300-μg 1:1000 epinephrine, and 750-mg cefuroxime. At the end of surgery, a continuous femoral nerve block (0.2% ropivacaine solution at 5 mL/h) and intravenous patient-controlled analgesia (2000 μg fentanyl in 0.9% saline, total volume of 100 mL, lockout time of 10 minutes, bolus 1 mL, no basal infusion) were administered.

2.4. CSF immunoassays

CSF was obtained twice at a 1-week interval at the time of spinal anesthesia. Five milliliter of CSF was collected between 7:00 AM and 10:00 AM to minimize fluctuations of biomarker levels.

2.5. *Measurement of S100B in CSF

The Human S100B enzyme-linked immunosorbent assay kit (Millipore, Milford, MA) was used to measure S100B levels in CSF samples, according to the manufacturer's protocol. Briefly, CSF samples were diluted 10-fold in the assay buffer, and the S100B standards were reconstituted with distilled water and serially diluted in the assay buffer. The standards, quality controls, and CSF samples were added with matrix solution to the appropriate wells preceded by the plate prewash step. The assay plate was sealed and set on a rotatory shaker for 2 hours. The plate was then washed with the wash buffer provided. The wash steps were aided by a HydroFlex microplate washer (Tecan, Männedorf, Switzerland). Diluted antibody-detection solution was added and incubated for 1.5 hours on the rotatory shaker. After the incubation, the plate was washed with wash buffer. The enzyme solution was added to each well and incubated for 30 minutes. After the incubation, the plate was washed with wash buffer. The substrate solution was added, and the stop solution was added to each well after 25 minutes. Absorbance at a wavelength of 450 nm were measured with a Victor3 multilabel reader (Perkin Elmer, Waltham, MA). The optical density values were converted to digital data with the Wallac 1420 Workstation software (Perkin Elmer). S100B levels were calculated based on a standard curve.

2.6. Measurement of $A\beta_{1–42}$, total tau, and phosphorylated tau in CSF

The INNO-BIA AlzBio3 kit (Fujirebio Europe, Gent, Belgium) was used to quantify $A\beta_{1–42}$, total tau (T-tau), and phosphorylated tau (P-tau181P) in CSF. The levels of $A\beta_{1–42}$, T-tau, and P-tau181P in CSF were measured by performing the multiplex assay following the manufacturer's protocol. Briefly, the beads provided were sonicated for 3 minutes with an ultrasonic cleaner (Fisher Scientific, Leicestershire, UK) and diluted in the diluent provided. The AlzBio3 Standards and Controls were thawed and vortexed. Conjugate 1 was diluted in diluent to prepare the Conjugate 1 Working Solution. After all reagents had been

prepared, the filter plate was washed with the wash buffer provided; the aspiration process was aided by a Bio-Plex Pro II wash station (Bio Rad, Hercules, CA). The diluted bead mix was added to the filter plate, and the buffer was aspirated. The CSF samples, standards, and controls were added to the filter plate with the Conjugate 1 Working Solution. The filter plate was set on an orbital shaker and incubated overnight at room temperature. The next day, the filter plate was washed with wash buffer and the Conjugate Working Solution for detection was added immediately to the plate. After 1 hour incubation, the filter plate was washed and the Reading Solution provided was added immediately to the plate. Relative fluorescence units were read on a Luminex 200 (Bio Rad) and converted to Aβ1–42, total tau, and P-tau181P concentration levels with reference to a standard curve using the Bio-Plex Manager software (Bio Rad).

2.7. Statistical analysis

A sample size of 15 patients, comparable to a previous study of changes in biomarkers after anesthesia and surgery,[8] was initially planned. Data are expressed as means ± standard deviation. The Wilcoxon's signed-rank test was used to compare the neuropsychological tests and biomarker assay results. Baseline data and the data collected 1 week later were compared. A $P < 0.05$ was considered to indicate significance.

3. Results

The patients' characteristics are shown in Table 1. The patients showed poor performance in frontal executive function (forward digit span, semantic fluency, letter-phonemic fluency, and Stroop color reading) at the second neuropsychological assessment compared to that at the first neuropsychological assessment (Table 2).

The concentrations of CSF markers decreased. The S100B concentration decreased significantly 1 week after the operation compared to the basal value (638 ± 178 vs 509 ± 167 pg/mL) ($P =$ 0.019). Aβ$_{1–42}$, T- tau, and P-tau181P levels tended to decrease, albeit not significantly so (Fig. 1).

4. Discussion

Our results show that the patients exhibited a decline in frontal-executive functions at 1 week post TKA. The S100B concentration decreased significantly 1 week after the operation compared to the basal value. Aβ$_{1–42}$, T-tau, and P-tau181P levels tended to decrease but the changes were not significant.

This study differed from a previous work in that it was performed in patients undergoing TKA with spinal anesthesia. In our study, the decrease in frontal-executive function was dominant. In the previous

Table 1

Demographic data.

Number	15
Age	73 ± 5
Height, cm	149 ± 5
Weight, kg	64 ± 8
Body mass index	29 ± 4
American Society of Anesthesiologists Physical Status, I/II	2/13
Duration of anesthesia, min	155 ± 32
Duration of surgery, min	107 ± 29

Table 2

Neuropsychological results.

Neuropsychological test	Baseline	One week	P
Attention			
Forward digit span	6.4 ± 1.3	5.5 ± 0.9	0.027
Backward digit span	3.5 ± 1.2	2.9 ± 1.2	0.117
Language			
BNT	12.2 ± 2.2	12.9 ± 2.3	0.951
Visuospatial function			
RCFT: copying	28.3 ± 7.7	25.9 ± 8.0	0.023
Memory			
SVLT	19.9 ± 6.0	20.2 ± 5.9	0.359
SVLT delayed recall	7.2 ± 2.3	7.2 1.5	0.972
SVLT DI	83.5 ± 21.5	85.8 ± 8.6	0.394
RCFT: immediate recall	12.8 ± 7.2	13.6 ± 6.3	0.305
RCFT: delayed recall	12.3 ± 5.8	12.8 ± 6.4	0.506
RCFT DI	64.0 ± 30.7	79.7 ± 9.9	0.085
Frontal/executive function			
COWAT: animal	13.8 ± 2.2	11.7 ± 2.3	0.011
COWAT: phonemic fluency	8.3 ± 4.4	5.8 ± 3.5	0.001
Stroop test: word reading	111.8 ± 0.6	109.5 ± 9.6	0.655
Stroop test: color reading	82.5 ± 21.5	71.3 ± 24.6	0.041

BNT = Boston naming test, COWAT = controlled oral word association test, RCFT = Rey–Osterrieth complex figure test, SVLT = Seoul verbal learning test.

work, postsurgical cognitive impairment occurred in both the executive and memory domains at discharge or 3 months after surgery.[4] In that study, the type of surgery and anesthesia were not clarified. The role of anesthesia in the development of POCD remains obscure. Some studies have reported no difference in cognitive functions between patients undergoing general and regional anesthesia in a systematic review,[9] whereas others reported that general anesthesia was marginally associated with POCD in a meta-analysis.[10] We suppose that no consideration of the type of disease entity made for such different results. Although the Mini Mental State Examination (MMSE) is widely used to confirm POCD,[11] it is not a very descriptive tool for assessing perioperative cognition or specific cognitive dysfunction because it was developed to diagnose patients with dementia, which is a state of relatively severe cognitive impairment. The MMSE includes questions about orientation, word recall, attention, calculation, language skills, and the ability to follow complex commands. We used more comprehensive neuropsychological tests to identify the type of cognitive decline.

The S100B CSF level decreased 1 week after surgery. The S100B protein is released after neuronal damage, such as after a head injury[12] or cardiopulmonary bypass.[5] Serum levels of S100B increase after general anesthesia and total hip replacement surgery.[13] The levels of S100B are significantly higher in patients with POCD compared to those without; thus, S100B may be associated with POCD.[13] The decrease in the level of S100B showed that TKA under regional anesthesia might not cause neuronal injury. Frontal dysfunction may be associated with other causes, such as environmental factors or medications. It is unclear why the S100B level decreased after knee surgery in our study. The CSF S100B concentration increases during mild or moderate depressive episodes,[14] whereas it decreases after antidepressant treatment in patients with a mood disorder.[15] It is possible that pain relief affects the level of S100B. A decrease in S100B may be associated with a multimodal analgesic strategy to maintain numeric rating pain scores < 4. Although surgery is related to the rate of cortical atrophy, the effect is temporary, and anatomical changes are reversible in specific brain areas.[16] Surgeries that frequently decrease pain and inflammation have
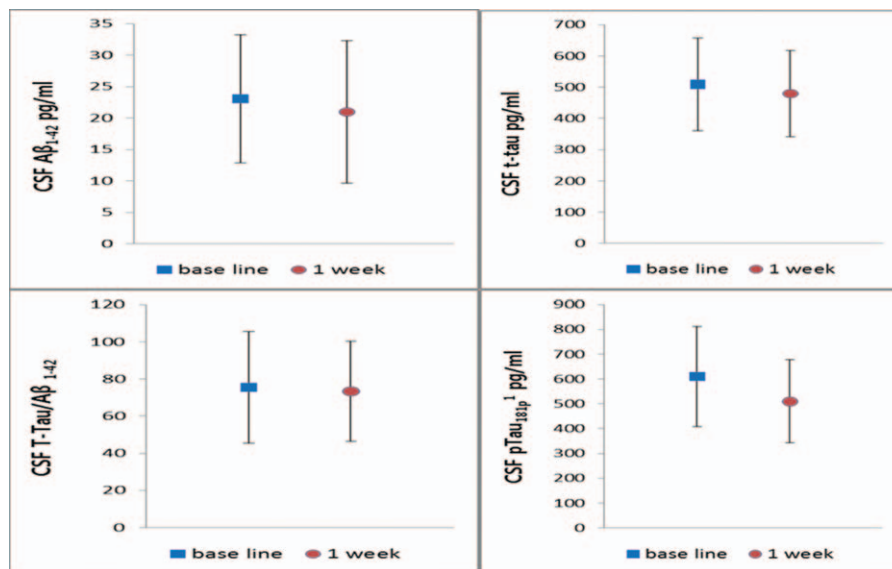
Figure 1. Changes in Alzheimer biomarkers in the cerebrospinal fluid before and 1 week after total knee arthroplasty. No significant changes are shown.

been associated with life-quality enhancement and cognitive improvement. Patients who receive joint replacement surgery show postoperative cognitive improvement and life-quality enhancement.[17] Neuroimaging studies have suggested that resolution of pain and inflammation may lead to neuroanatomical changes and cognitive improvement.[18] The improvement in quality of life might explain the decrease in S100B.

In this study, the tau protein levels decreased but the change was not significant. CSF P-tau181P is one of the most sensitive biomarkers of cognitive decline in initially cognitively normal patients.[19] In contrast to our findings, the CSF tau concentration increased 1 week after a cardiac surgical intervention.[5] This result could be explained by the high incidence of POCD after cardiac surgery under general anesthesia. The incidence of POCD was higher in a general anesthesia group compared with that in a regional anesthesia group.[20] Furthermore, cardiac surgery is associated with more POCD than total hip surgery at 7 days post-procedure.[21] Our study had several limitations. First, lumbar CSF measures of biomarker levels may not be the most accurate measure of biomarker changes in the brain. However, there is no alternative method of measuring CSF biomarkers in a clinical setting. Obtaining CSF is a challenging procedure. Bilateral TKA was appropriate for this study, as it was part of patient care. Second, long-term follow-up, which may have shown the course of frontal dysfunction, was not performed. We performed this study to investigate POCD after TKA; further research is required to reveal the consequences of frontal dysfunction. In conclusion, we suggest that frontal-executive function can be affected 1 week after surgery in patients undergoing TKA with spinal anesthesia, but the cognitive decline is not definite. The analysis of CSF biomarkers showed that TKA under regional anesthesia might not cause neuronal injury. Frontal dysfunction after TKA may be associated with other causes.

Acknowledgments

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