



Risk factors for postoperative delirium following total knee arthroplasty in elderly patients

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Background: Postoperative delirium has been suggested as a significant predictor of postoperative morbidity and mortality in elderly patients. They usually have multiple comorbidities, including cardiovascular, respiratory, renal, and neurologic disease. We aimed to determine the incidence rate and modifiable risk factors of postoperative delirium following total knee arthroplasty in elderly.

Methods: We reviewed the medical records of 318 elderly patients (age >65 years) underwent unilateral total knee arthroplasty between 2009 and 2016. Patient demographics, American Society of Anesthesiologists physical status, preoperative comorbidities, type and duration of anesthesia and surgery, length of hospital stay, ambulation ability, frequency of intraoperative hypotension, frequency of hypothermia, whether the patient was transfused or heparinized, and perioperative laboratory results were evaluated. Univariate and multivariate logistic regression analyses were used to identify significant independent predictors of postoperative delirium.

Results: The incidence rate of postoperative delirium was 6% in this study. Univariate analysis showed that postoperative delirium was significantly associated with age, body mass index, general anesthesia, anesthesia time, preoperative dementia, intraoperative hypotension, preoperative hemoglobin, blood transfusion, and intraoperative hypothermia. Preoperative dementia (odds ratio [OR] = 8.80), intraoperative hypotension (OR = 1.06), and preoperative hemoglobin (OR = 0.66) were significant independent risk factors of postoperative delirium.

Conclusions: Preoperative dementia is the most important risk factor of postoperative delirium. High-risk patients undergoing total knee arthroplasty should be thoroughly evaluated and their dementia should be managed preoperatively. Adequate management of preoperative hemoglobin and intraoperative hypotension might also be helpful in reducing the incidence of postoperative delirium in this population.

Key Words: Aged, Anesthesia, Delirium, Knee replacement arthroplasty, Postoperative complications.

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INTRODUCTION

The incidence of postoperative delirium following general surgery ranges from 5% to 10% in the general population and

10% to 15% in the elderly [1]. The incidence of postoperative delirium depends upon the type of surgery. In those undergoing elective orthopedic surgery, the incidence varies from 9% to 15% [2]. Other studies have reported an incidence of

postoperative delirium from 7% to 75% in patients who underwent total joint arthroplasty [3,4].

Total knee arthroplasty is an effective and safe procedure in patients with osteoarthritis [5]. Together with total hip replacement, these are the most common orthopedic procedures [6]. About 61,439 Koreans (9,029 men and 52,410 women) underwent total knee arthroplasty in 2016, and of these, 48,244 (88.5%) were aged 65 years or above¹⁾ (7,301 men and 44,241 women). The current population aged 65 years and above in Korea is around 6.57 million (13.2% of the total population); this number is 2.25 times more than it was in 2010 (11% of the total population). The ratio between the elderly and the young (0–14 years old) populations has also risen from 0.68 in 2010 to 0.95 in 2016 [7].

The pathophysiology of delirium is not well-understood, and preventive and therapeutic measures are lacking [8,9]. Assessment of preexisting risk factors of postoperative delirium is an important part of the perioperative care in elderly patients. Postoperative delirium is associated with longer hospital stays, delayed rehabilitation, cognitive dysfunction, higher health care costs, and increased mortality [10,11]. The aim of this study was to determine the prevalence of postoperative delirium after total knee arthroplasty in elderly patients and identify which factors might contribute to its development.

MATERIALS AND METHODS

This study was conducted with the approval of the Institutional Review Board of our institute (SGPAIK2016-08-015). The subjects were patients aged 65 years and above who underwent total knee arthroplasty under either general or regional anesthesia between March 2009 and June 2016. We excluded patients with multiple trauma, metastatic malignant tumors, and those undergoing reoperations. Finally, a total of 318 out of 430 eligible patients were included in the study. The collected data were limited to the patients' medical records from their hospitalization for surgery. The incidence of postoperative delirium was used as the primary outcome variable. The incidence of postoperative delirium was limited to cases in which the patient's symptoms met the criteria of

the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) in consultation with a psychiatric specialist. The demographics (sex, age, height, and weight), American Society of Anesthesiologists physical status, alcohol history (number of drinks per week), smoking history (cigarettes per day, duration of smoking), other comorbidities (pre-existing dementia, delirium, hypertension, pathological arrhythmia, myocardial infarction, cardiac valvular disease, cardiomyopathy, chronic obstructive pulmonary disease, asthma, diabetes, acute or chronic renal failure, liver disease, cerebrovascular disease, and neurological disease) were evaluated through a retrospective review of the medical records. We also evaluated postoperative mortality, length of hospitalization, admission to an intensive care unit, type and duration of anesthesia, type of surgery, use and type of sedation during regional anesthesia, blood transfusion, frequency of hypotension, and frequency of hypothermia. Dexmedetomidine or midazolam was used for sedation during regional anesthesia. Hypotension was defined as an absolute systolic blood pressure below 90 mmHg occurs 3 times. Body temperature was measured using an esophageal temperature stethoscope or tympanic thermometer, and hypothermia was defined as below 36.0°C. All patients in this institute underwent routine postoperative analgesia using the following protocols: after admission to the post-anesthesia care unit, pain intensity was evaluated by a numeric rating scale (NRS, 0 to 10). If the NRS was above 5, intravenous fentanyl 1 µg/kg was repeatedly administrated until the patient's NRS dropped below 4. Oxycodone- and nefopam hydrochloride-based patient-controlled intravenous analgesia were also provided continuously for all patients.

Statistical analysis

The data are presented as the mean ± standard deviation, number of patients (percentage), or number (95% confidence interval [CI]; lower to upper bound). The R for windows version 3.2.0 (R Foundation for Statistical Computing, Austria) was used for the statistical analyses. A logistic regression analysis based on a binomial generalized linear model was performed to identify the factors affecting postoperative outcomes.

In order to identify significant independent predictors of postoperative delirium, univariate (cut-off value was $P < 0.2$)

¹⁾2016 Korea health care big data hub (<http://opendata.hira.or.kr/home.do>)

and multivariate logistic regression analyses were used. For the univariate analysis, patient demographics, American Society of Anesthesiologists physical status, preoperative comorbidities, type and duration of anesthesia and surgery, interval between injury and surgery, length of hospital stay, ambulatory ability, frequency of intraoperative hypotension, frequency of hypothermia, whether the patient was transfused or heparinized, and perioperative laboratory results were evaluated. Odds ratios (OR) and 95% CI were reported for both univariate and multivariate analyses.

Age, height, body weight, history of dementia, general anesthesia, anesthetic time, hypotension frequency, postoperative hemoglobin, and whether the patient was transfused were considered as possible independent variables for postoperative delirium and were analyzed using multivariate logistic regression. The items with P values less than 0.05 in the multivariate analysis were considered statistically significant.

For producing the final reduced logistic regression model, we used a stepwise selection method. The C-statistic and the Hosmer-Lemeshow goodness-of-fit test were used to assess the fitness of the logistic regression model.

RESULTS

Characteristics and perioperative data

A total of 318 patients were included in the study. Table 1 outlines several differences in demographic characteristics between the two groups. Postoperative delirium was present in 19/318 patients (6.0%). The delirium group (patients with postoperative delirium) had longer anesthetic durations and hospital stays than the non-delirium group (patients without postoperative delirium). The results indicated that prevalence of history of dementia was significantly higher in

Table 1. Comparison of Demographics and Characteristics of Patients with/without Postoperative Delirium

Variable		No delirium (n = 299)	Delirium (n = 19)	P value
Sex	Female	263 (88.0)	16 (84.2)	0.903
	Male	36 (12.0)	3 (15.8)	
Age (yr)		76.0 ± 5.6	78.4 ± 6.2	0.067
Height (cm)		153.7 ± 8.7	152.3 ± 9.1	0.505
Weight (kg)		60.5 ± 10.8	60.2 ± 11.9	0.923
Days of hospitalization (d)		20.1 ± 16.0	31.3 ± 22.5	0.045
Mortality		0 (0.0)	1 (5.3)	0.063
ASA PS	I	11 (3.7)	0 (0.0)	0.773
	II	227 (75.9)	14 (73.7)	
	III	60 (20.1)	5 (26.3)	
	IV	1 (0.3)	0 (0.0)	
Anesthesia	General	76 (25.4)	8 (42.1)	0.183
	Regional	223 (74.6)	11 (57.9)	
Anesthesia time (min)		195.2 ± 57.2	221.6 ± 59.0	0.052
Type of surgery	TKRA	274 (91.7)	16 (84.2)	0.634
	Rev. TKRA	25 (8.3)	3 (15.8)	
Ambulatory	Yes	292 (97.7)	19 (100.0)	1.000
	No	7 (2.3)	0 (0.0)	
Sedation	Yes	128 (42.8)	8 (42.1)	1.000
	No	171 (57.2)	11 (57.9)	
Current smoker	Yes	6 (2.0)	1 (5.3)	0.895
	No	293 (98.0)	18 (94.7)	
Alcohol	Frequency/wk	0.8 ± 3.6	1.2 ± 4.6	0.608
Preoperative Hb (mg/dl)		13.0 ± 1.3	12.2 ± 1.7	0.013
Preoperative dementia	Yes	6 (2.0)	16 (84.2)	0.005
	No	293 (98.0)	3 (15.8)	
Intraoperative-hypotension	Yes	60 (20.1)	10 (52.6)	0.002
	No	239 (79.9)	9 (47.4)	

Values are expressed number of patient (%) or mean ± SD.

ASA PS: American Society of Anesthesiologists physical status, TKRA: total knee replacement arthroplasty, Rev.: revision, Hb: hemoglobin.

the delirium group (16/19, 84.2%) than in the non-delirium group (6/299, 2.0%). The frequency of hypotension was also significantly higher in the delirium group (52.6%) compared with the non-delirium group (20.1%). There was, however, no significant difference in the type of surgery, preoperative ambulatory ability, drinking, or smoking history between the two groups. The use of sedative drugs (dexmedetomidine or midazolam) in regional anesthesia also did not affect the rate of postoperative delirium (Table 1).

Univariate and multivariate analyses

The results of the logistic analysis performed to identify associations between different variables and postoperative delirium are presented in Table 2. Univariate analysis indicated that age, height, body weight, preexisting dementia, type of anesthesia, anesthetic time, frequency of intraoperative hypotension, preoperative hemoglobin level, intraoperative hypothermia, and whether the patient was transfused were factors that significantly correlated with the incidence of

postoperative delirium.

The full multivariate logistic regression model showed that the presence of preoperative dementia prior to surgery was significantly associated with postoperative delirium (OR = 6.22, 95% CI = 0.93–35.67) (Table 2). After stepwise variable selection, the final reduced logistic regression model showed that preoperative dementia (OR = 8.80, 95% CI = 1.55–42.38), the frequency of intraoperative hypotension (OR = 1.06, 95% CI = 0.99–1.13), and preoperative hemoglobin level (OR = 0.66, 95% CI = 0.46–0.94) were significantly associated with postoperative delirium (Table 3).

DISCUSSION

This study showed that the prevalence of postoperative delirium after total knee arthroplasty in elderly patients aged 65 years and above was 6.0% (n = 19/total 318 patients). The incidence of postoperative delirium can vary from study to study, and these differences seem to be based on the diagnostic methods used. Chung et al. [12] used trained research

Table 2. Full Logistic Regression Model for the Risk Factors of Postoperative Delirium in Elderly Patient under Total Knee Arthroplasty Using Variables Which Obtained through Univariate Analysis

Variable	Estimate	Std. Error	z value	Pr(> z)	OR	Lcl	Ucl
(Intercept)	-7.4595	7.3564	-1.01	0.3106	0.00	0.00	776.36
Age (yr)	0.0585	0.0486	1.20	0.2290	1.06	0.96	1.17
Height (cm)	0.0075	0.0279	0.27	0.7884	1.01	0.96	1.07
Body weight (kg)	0.0186	0.0236	0.79	0.4300	1.02	0.97	1.07
Preoperative dementia	1.8277	0.9068	2.02	0.0438	6.22	0.93	35.67
General anesthesia	0.5763	0.6290	0.92	0.3595	1.78	0.51	6.15
Anesthesia duration (min)	0.0040	0.0049	0.82	0.4150	1.00	0.99	1.01
Frequency of intraoperative hypotension*	0.0624	0.0347	1.80	0.0719	1.06	0.99	1.14
Preoperative Hb (g/dl)	-0.3602	0.1951	-1.85	0.0649	0.70	0.47	1.02
Transfusion (yes)	0.6873	1.1363	0.60	0.5452	1.99	0.30	39.97
Intraoperative hypothermia (< 36)	0.7855	1.2300	0.64	0.5231	2.19	0.26	50.12

Std.: standard, OR: odds ratio, Lcl: low boundary of 95% confidence limit, Ucl: upper boundary of 95% confidence limit, Hb: hemoglobin. Cut-off value from univariate analysis of each variable is $P < 0.2$. *Hypotension was defined by systolic blood pressure less than 90 mmHg.

Table 3. Logistic Regression Model for the Risk Factors of Postoperative Delirium in Elderly Patient under Total Knee Arthroplasty (Reduced Final Model)

Variable	Estimate	Std. Error	z value	Pr(> z)	OR	Lcl	Ucl
(Intercept)	2.1050	2.2357	0.94	0.3464	8.21	0.09	634.97
Preoperative dementia	2.1743	0.8194	2.65	0.0080	8.80	1.55	42.38
Frequency of intraoperative hypotension	0.0604	0.0307	1.97	0.0487	1.06	0.99	1.13
Preoperative Hb	-0.4116	0.1795	-2.29	0.0218	0.66	0.46	0.94

Std.: standard, OR: odds ratio, Lcl: low boundary of 95% confidence limit, Ucl: upper boundary of 95% confidence limit, Hb: hemoglobin. Hypotension was defined as if systolic blood pressure less than 90 mmHg.

members to screen for delirium symptoms and confirmed the diagnosis of postoperative delirium with a psychiatrist; the prevalence of delirium in that study was 3.1%. Radcliff et al. [13] used trained research members to confirm the diagnosis of postoperative delirium and the prevalence was higher (10.4%). In this study, the diagnosis was limited to cases in which the patient's symptoms met the DSM-V criteria in consultation with a psychiatric specialist.

Previously known risk factors for postoperative delirium include age, male sex, cognitive impairment, type and duration of surgery, general anesthesia, anesthetic time, postoperative pain, hypothermia, and blood transfusion [10]. Preoperative and postoperative hemoglobin, serum sodium levels, and postoperative PaO₂ are reported risk factors of postoperative delirium [14,15]. Postoperative pain is also known to be an important risk factor for postoperative delirium [16]. In this study, we found that preexisting dementia, the frequency of hypotension, and preoperative anemia were significantly associated with postoperative delirium. Although the pathologic relationship between dementia and delirium is not yet understood, many studies have investigated this significant correlation [17,18].

In this study, we also confirmed that the frequency of hypotension was associated with a higher incidence of postoperative delirium; however, the role of intraoperative hypotension in postoperative delirium remains controversial. Hirsch et al. [19] did not find a significant relationship between intraoperative hypotension or duration of hypotension and postoperative delirium in patients aged 65 years and above undergoing major non-cardiac surgery. However, meta-analysis of risk factors for postoperative delirium in gastrointestinal surgery identified that perioperative blood transfusion (OR = 3.2) and intraoperative hypotension (OR = 2.7) were both highly associated with postoperative delirium [20].

It is reported that anemia in elderly patients increases mortality and worsens their functional status [14]. Maldonado [21] have suggested that inadequate cerebral oxygenation may be the cause of delirium in severely ill patients who have an imbalance between oxygen supply and demand. Another recent study reported focal decrease of cerebral oxygenation could also be associated with cognitive dysfunction in elderly patients [22].

Decreased cerebral blood flow is influenced by hypotension and low hemoglobin levels, both of which impair oxygen

delivery. A study that used transcranial Doppler found that blood flow velocity in the middle cerebral artery is lesser in the delirium group than in the non-delirium group in patients with dementia [23]. This could, in part, account for the correlation between postoperative delirium and hypotension or anemia.

Several limitations of our study are due to its retrospective design. First, a relatively small number of patients was included in this study. Although 10 years' worth of medical records were used, this study was only conducted in one healthcare institution. Second, hypoactive delirium, wherein patients demonstrate reduced motor activity and sedation, is frequently less recognized than hyperactive, wherein delirium is often associated with psychotic features. Some studies have found that only 1.6% of intensive care unit patients experience pure hyperactive delirium, and hypoactive delirium is more common in patients aged 65 years and above [24]. This indicates that hypoactive delirium could be neglected and underestimated without careful monitoring using standardized scales to detect hypoactive or mixed-type delirium. Third, the results of this study are derived from only one type of surgery, making it difficult to generalize the findings to patients undergoing other surgeries. Fourth, we could not collect specific data on the duration and severity of pre-existing comorbidities, as this information was missing from the electronic medical records. Last is that postoperative delirium was only assessed during the hospitalization period; therefore, we might have missed delirium that occurred after patients were discharged.

In summary, we found that preoperative dementia is the most important risk factor of postoperative delirium. High-risk patients undergoing total knee arthroplasty should be fully evaluated, and when possible, dementia should be managed preoperatively. Adequate management of preoperative anemia and intraoperative hypotension might also be helpful in reducing the incidence of postoperative delirium in this population.

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