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ORIGINAL INVESTIGATION

Risk factors associated with treatment of hyperactive postoperative delirium in elderly patients following hip fracture surgery under regional anesthesia: a nationwide population-based study

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Abstract
Background and objectives: Delirium is common but is frequently undetected by clinicians, despite the fact that it can be life-threatening. This study aimed to identify the incidence of delirium and the preoperative factors associated with perioperative use of drugs to treat hyperactive delirium in elderly patients who underwent hip fracture surgery under regional anesthesia.
Methods: We retrospectively reviewed records of all patients ≥ 65 years of age who had undergone hip-fracture surgery under regional anesthesia, covered by the Korean National Health Insurance, between January 1, 2009 and December 31, 2015. A univariate and stepwise logistic regression model with the occurrence of hyperactive delirium as the dependent variable was used to identify the perioperative factors for this sample of patients.
Results: Among the 70,696 patients who underwent hip fracture surgery, 58,972 patients who received regional anesthesia were included in our study; of these, perioperative use of drugs to treat hyperactive delirium was diagnosed in 8,680 (14.7%) patients. Performing stepwise logistic regression, preoperative variables found to be associated with delirium were: male sex, age ≥ 85 years, hospital type (medical center), ICU and ventilator care, the presence of a neurodegenerative disorder, uncomplicated diabetes mellitus, peptic ulcer disease, and previously diagnosed psychoses and/or depression (OR = 1.49 [1.42–1.58], 4.7 [4.15–5.37], 13.3 [7.57–23.8], 1.52 [1.43–1.60], 1.19 [1.01–1.40], 1.20 [1.14–1.27], 1.09 [1.04–1.14], 0.87 [0.96–0.00], 2.23 [1.48–3.37], and 1.38 [1.32–1.46], respectively).

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Conclusions: Postoperative hyperactive delirium may affect approximately 15% of elderly patients submitted to hip fracture repair under regional anesthesia. This study has identified multiple preoperative risk factors associated with postoperative hyperactive delirium and its pharmacological management strategies.

Introduction

With a rapidly aging population, the incidence of hip fracture continues to increase in South Korea.[1] Elderly patients who fracture their hips suffer adverse complications, including mortality, thus posing a medical and financial burden on society.[2] Although there have been improvements in surgical and anesthetic care over time, morbidity and mortality after hip fracture remain high.[3] One of the most common complications following hip fracture surgery is delirium, with a reported incidence rate between 4% and 53%.[4]

Delirium is common but frequently remains undetected by clinicians even though it can be life-threatening and give rise to serious preventable complications.[5] Postoperative delirium is known to be associated with increased length of ICU and hospital stay, increased hospital costs, and mortality after surgery.[6]

To decrease the mortality and morbidity including postoperative delirium, it is recommended that the type of anesthesia used in hip fracture surgery should be considered. The effects of the type of anesthesia on outcomes in elderly patients are debated; some studies have reported that the use of regional anesthesia (RA) yields a more favorable outcome while other studies report no difference in the outcome. Despite the favorable results of RA in hip fracture surgery, delirium still occurs. Thus, the risk factors for delirium require investigation so that postoperative complications can be reduced in geriatric patients. The objective of this study was to identify the incidence of hyperactive delirium and the preoperative factors associated with hyperactive delirium in elderly patients who underwent hip fracture surgery under regional anesthesia.

Methods

This study was reviewed and approved by the institutional review board (IRB Nº 2019-05-005), and the need to obtain informed consent was waived because we used de-identified administrative data.

The NHIS is a single health insurer managed by the Korean government and covering approximately 97% of Koreans. The remaining 3% of Koreans are covered by the Medical Aid Program (MAP).[7] The National Health Information Database (NHID), created by the NHIS, is a public database composed of data obtained between 2002 and 2015 on the health care utilization, health screening, sociodemographic variables, and mortality for the entire South Korean population, composed of data obtained between 2002 and 2015. The NHID is open to all researchers whose study protocols are approved by the official review committee. The NHID provides data for research activity across various sectors, such as the social, economic, environmental, and industrial sectors, as well as for the policy and medical sectors, in the form of the Sample cohort database, Customized database, Health Disease index, and others. Among these services, our data were ''customized health information data'', provided upon request specifically for our study.

Participants

We included all patients $\geq$ 65 years old who underwent hip surgery under regional anesthesia in hospitals in Korea between January 1, 2009 and December 31, 2015 (based on admission date). The inclusion and exclusion criteria used were as follows:

Inclusion criteria

Principal diagnosis upon admission of the femoral neck (S720) or trochanteric fracture (S721) based on the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code; admission with at least one of the following surgical operations based on procedure codes: Open Reduction of Fractured Extremity [Femur], Total Arthroplasty [Hip], or Hemiarthroplasty [Hip]; patients who received both spinal and epidural anesthesia

Exclusion criteria

Patients with a diagnosis of multiple traumas or fractures (''S00–S70'', ''S73–99'', ''T07'', or ''T14''); patients who underwent more than two such operations during the same admission period; patients who had a diagnosis of psychiatric disease (F10–F29) and medication history of haloperidol, risperidone, and/or quetiapine prior to admission.

Hyperactive delirium was defined as a record of intravenous administration of haloperidol, risperidone, and quetiapine at least once during the hospitalization.

Independent variables

The patient characteristics recorded included sex, age, comorbid conditions, and hospital type (medical center = 1, general hospital = 2, or clinic = 3). The Elixhauser Comorbidity method, which outperforms the Charlson Index in predicting inpatient death after orthopedic surgery, was used to identify patient comorbidities.[8] Elixhauser Comorbidity measures were calculated by the sum of weighted points based on the presence or absence of 31 different medical conditions. These include congestive

heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, complicated and uncomplicated hypertension, paralysis, other neurologic disorders, chronic pulmonary disease, complicated and uncomplicated diabetes mellitus, hypothyroidism, renal failure, liver disease, peptic ulcer disease, HIV infection/AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression. The comorbidities were followed using the list of ICD-10 codes defined by Quan et al.[9] Stays in the intensive care unit (ICU), as well as ventilator care, were also recorded.

Statistical analysis

All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Groups were compared using the Mann–Whitney U test; descriptive variables were analyzed by chi-squared analysis. Two-tail *p*-values were used throughout the analysis, and 95% confidence intervals were reported with relative risks and odds ratios for variables significantly associated with delirium. Using a univariate and stepwise logistic regression model with the occurrence of delirium as the dependent variable, perioperative factors were identified for this sample of patients. Stepwise logistic regression was performed with variables, which were statistically significant following the univariate logistic regression. All statistical testing was two-sided with a significance level of 0.05. For continuous variables, data are presented as the median (range).

Results

We identified 70,696 patients who were admitted to the hospital during 2009–2015, were ≥ 65 years old, and underwent surgery for hip fracture under regional anesthesia; of these, 363 patients were excluded due to missing data. To reduce confounding bias, 11,361 patients with a concomitant diagnosis of psychiatric disease (F10–F29) and/or who had a medication history of haloperidol, risperidone, and/or quetiapine before admission were excluded. After these exclusions, 58,972 patients remained for inclusion in our study (Fig. 1).

The incidence of hyperactive delirium in patients who underwent hip-fracture surgery under regional anesthesia was 14.7% (8680/58972). Sex, age, Elixhauser Comorbidity score, and hospital type were different between the two groups (Delirium vs. No delirium, Table 1). Covariates including congestive heart failure, cardiac arrhythmia, peripheral vascular disorder, complicated and uncomplicated hypertension, neurologic disorder, uncomplicated diabetes mellitus, renal failure, fluid and electrolyte disorder, deficiency anemia, psychoses, and depression showed significant differences between the groups (Table 1). Additionally, ICU stays, ventilator care, and mortality were significantly different between the groups (Table 1).

Univariate factors associated with hyperactive delirium included male sex (OR = 1.26 [1.19–1.33]), age ≥ 85 (OR = 4.5 [4.0–5.1]), Elixhauser Comorbidity score ≥ 15 (OR = 1.3 [1.14–1.48]), hospital type 1 (OR = 26.8 [9.25–28.6]), congestive heart failure (OR = 1.15 [1.09–1.21]), cardiac arrhythmia (OR = 1.15 [1.09–1.21]), perivascular disease (OR = 1.05 [1.0–1.1]), uncomplicated hypertension (OR = 1.12 [1.05–1.19]), complicated hypertension (OR = 1 [0.0–9.25]), neurodegenerative disorder (OR = 1.26 [1.26–1.33]), uncomplicated diabetes mellitus (OR = 1.02 [1.00–1.10]), renal failure (OR = 1.15 [1.06–1.24]), fluid disorder (OR = 1.07 [1.01–1.12]), deficiency anemia (OR = 1.06 [1.0–1.11]), psychoses (OR = 2.44 [1.64–3.62]), and depression (OR = 1.33 [1.27–1.39]). Duration of ICU stay (OR = 2.13 [2.02–2.25]) and ventilator care (OR = 1.99 [1.7–2.3]) were also significant risk factors for hyperactive delirium (Table 2).

After adjusting for other factors by stepwise logistic regression, male sex (OR = 1.49 [1.42–1.58]), age ≥ 85 (OR = 4.7 [4.15–5.37]), hospital type 1 (OR = 13.3 [7.57–23.8]), ICU stay (OR = 1.52 [1.43–1.60]), ventilator care (OR = 1.19 [1.01–1.40]), neurologic disorder (OR = 1.20 [1.14–1.27]), uncomplicated diabetes mellitus (OR = 1.09 [1.04–1.14]), peptic ulcer disease (OR = 0.87 [0.96–0.00]), psychoses (OR = 2.23 [1.48–3.37]), and depression (OR = 1.38 [1.32–1.46]) remained predictive for hyperactive delirium (Table 3).

Discussion

The present study reports that hyperactive delirium which needs pharmacologic intervention could occur in approximately 15% of elderly hip-fracture surgery cases in which regional anesthesia is used. Multiple preoperative risk factors, including male sex, age ≥ 85, hospital type (medical center), ICU and ventilator care, neurodegenerative disorder, uncomplicated diabetes mellitus, peptic ulcer disease, psychoses, and depression, were associated with hyperactive delirium.

Elderly hip fracture patients require efficient, multidisciplinary perioperative evaluation and management to improve postoperative outcomes. The most common complication after hip fracture surgery is delirium, reported in up to 53% of the cases.[4] However, in our study, the incidence of delirium requiring pharmacological intervention in our population was 14.7%. The difference between these reported incidence rates may be related to the definition of delirium and the anesthetic method used.

Several previous reports compared the use of general anesthesia and regional anesthesia to reduce morbidity and mortality, including delirium. They reported that regional anesthesia yielded more favorable outcomes than general anesthesia.[3,10,11] Therefore, we selected only patients who underwent regional anesthesia to reduce selection bias. It is known that regional anesthesia is associated with shorter times for mobilization and positive outcomes.[12] Even regional anesthesia can cause delirium requiring pharmacological intervention to some extent. Therefore, the ability to detect patients who have a high risk of postoperative hyperactive delirium which needs pharmacologic intervention following hip surgery will reduce the incidence of delirium and help with its prevention.

Our results are consistent with those of previous studies. In line with previous reports, age ≥ 85 years was a

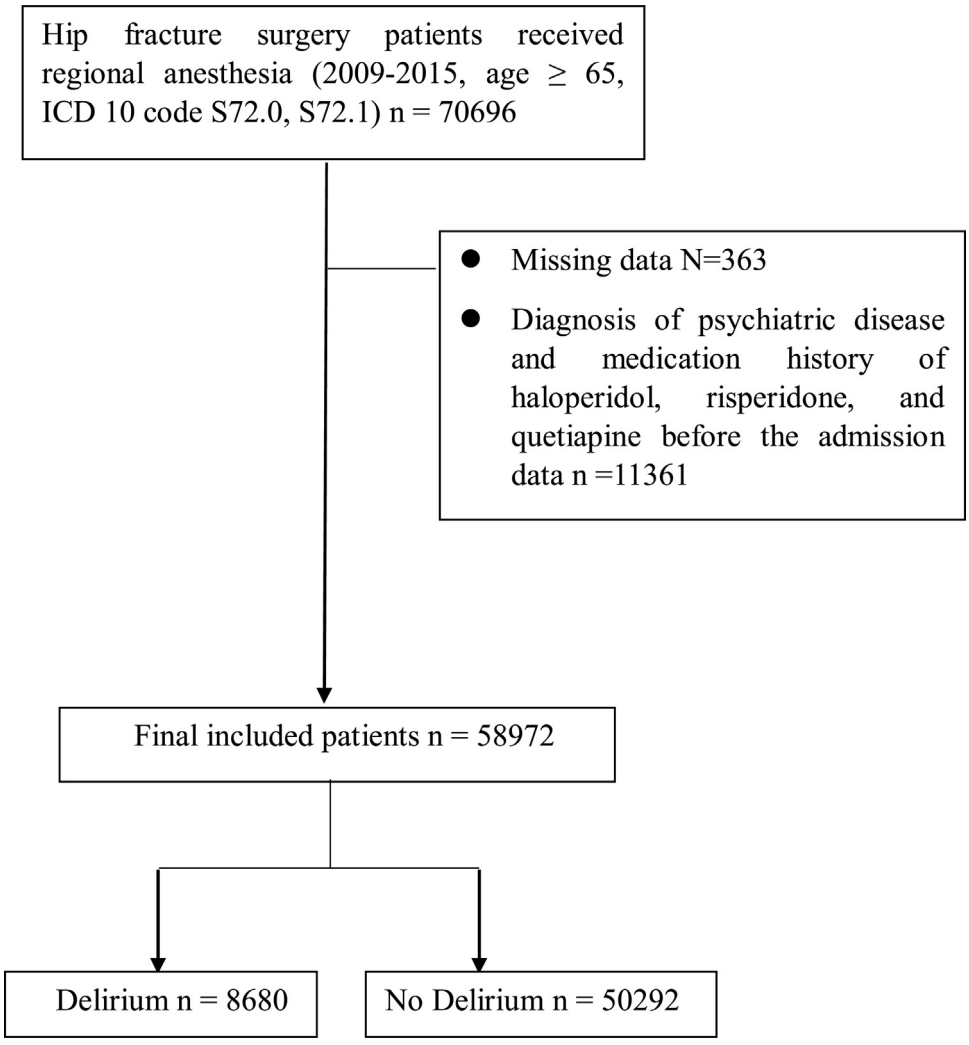

Fig. 1 Flow diagram.

significant predictor of hyperactive delirium. It is further suggested that age ≥ 85 could be the cutoff for hyperactive delirium prevalence. Additionally, male patients had more developed delirium, similar to the study by Edelstein et al., which reported that the incidence of delirium in male patients was twice of that reported in females.[13]

Our study found that not only preoperative variables such as age, male sex, and comorbidities such as preoperative neurodegenerative disorder, diabetes mellitus, peptic ulcer disease, psychoses, and depression but also ICU stay and ventilator care may have strong associations with delirium. There are many known risk factors for delirium including the predisposing factors such as neurodegenerative disorder, depression, and comorbidity or severity of illness.[14] Duration of ICU stay and mechanical ventilation are also well known precipitating factors of delirium.[15,16] According to a recent study, peptic ulcer disease is associated with mental health problems, which suggests a possible role of the brain-gut axis system and the hypothalamic-pituitary-adrenal axis; however, further detailed evaluations are required to confirm their role.[17]

According to a meta-analysis of elderly hip fracture cases, patients with postoperative delirium had more than twice the risk of mortality than those without delirium.[18] Identification of patients who have a high risk of postoperative delirium will decrease both the prevention and treatment strategies, and help improve the hip fracture surgery outcomes.

The strength of this study was its use of anonymized data from nearly an entire country's population, which made its results less susceptible to selection bias. Additionally, we only selected patients who had received RA to reduce the influence of other types of anesthesia.

Nevertheless, this study had some limitations; first, this study used retrospective national claims data, and thus, the patient's clinical data were not included. Second, claims data can contain coding errors.[19] Third, information on diagnosis and disease included in the healthcare utilization database may not have sufficient validity for identifying disease occurrence and prevalence, since the data have not been analyzed and coded for research purposes, but rather for medical services claims and reimbursements. Fourth, several variables control the confounding factors which

Table 1 Patient characteristics.

	Delirium (n = 8680)	No delirium (n = 50,292)	*p*-value
Sex (male/female)	2399/6281	11,718/38,574	<.0001*
Age (0/1/2/3/4)	279/835/1766/2447/3353	4426/8962/12,711/12,414/11,779	<.0001*
Elix (0/1/2/3)	1845/4020/2490/325	11,497/24,115/13,137/1543	<.0001*
Hospital type (1/2/3)	6931/1737/12	31,873/17,516/903	<.0001*
ICU care	2401(27.6)	7651(15.2)	<.0001*
Ventilator care	215(2.5)	635(1.3)	<.0001*
Congestive heart failure	2785(32.1)	14,619(29.1)	<.0001*
Cardiac arrhythmias	2259(26.0)	11777(23.4)	<.0001*
Peripheral vascular disorders	4599(52.9)	25,954(51.6)	0.0177*
Complicated hypertension	3060(35.3)	16,874(33.5)	0.002*
Neurodegenerative disorders	2151(24.8)	10,361(20.6)	<.0001*
DM, uncomplicated	4845(55.8)	27,416(54.5)	0.0242*
Renal failure	748(8.6)	3808(7.6)	0.0008*
Peptic ulcer disease, no bleeding	5453(62.8)	32,120(63.8)	0.0616
Rheumatoid arthritis/collagen vascular disease	3070(35.4)	18,303(36.4)	0.0666
Weight loss	3767(7.5)	700(8.1)	0.0619
Fluid and electrolyte disorders	13,262(23.4)	2418(27.9)	0.0038*
Psychosis	35(0.4)	84(0.17)	<.0001*
Depression	4098(47.2)	20,195(40.1)	<.0001*

Age 0, aged 65–70 years; Age 1, aged 70 –75 years; Age 2, aged 75–80 years; Age 3, aged 80–85 years; Age 4, aged ≥ 85 years. Hospital type 1, medical center; Hospital type 2, general hospital; Hospital type 3, clinic. Elixhauser 1, Elixhauser < 5; Elixhauser 2, Elixhauser 5–9; Elixhauser 3, Elixhauser ≥ 10. ICU, intensive care unit. Values are expressed as absolute number (percentages), or absolute number.
* $p < 0.05$ between-groups comparison.

Table 2 Univariate analysis.

	Odds Ratio	95% confidence interval	*p*-value
Sex	0.794	0.754–0.836	<.0001*
Age	4.509	3.971–5.118	<.0001*
Elixhuser comorbidities	1.299	1.142–1.478	<.0001*
Hospital type	0.061	0.035–0.108	<.0001*
ICU care	2.132	2.022–2.248	<.0001*
Ventilator care	1.994	1.706–2.332	<.0001*
Congestive heart failure	1.15	1.095–1.208	<.0001*
Cardiac arrhythmias	1.148	1.09–1.21	<.0001*
Peripheral vascular disorders	1.055	1.008–1.104	0.0219*
Complicated hypertension	1.121	1.054–1.192	0.0003*
Neurodegenerative disorders	1.265	1.2–1.335	<.0001*
DM, uncomplicated	1.052	1.005–1.101	0.0313*
Renal failure	1.147	1.057–1.245	0.001*
Peptic ulcer disease, no bleeding	0.954	0.91–0.999	0.0518
Rheumatoid arthritis/collagen vascular disease	0.953	0.909–0.999	0.0478*
Weight loss	1.084	0.996–1.179	0.0607
Fluid and electrolyte disorders	1.072	1.019–1.128	0.0074*
Psychosis	2.437	1.642–3.618	<.0001*
Depression	1.33	1.27–1.392	<.0001*

ICU, intensive care unit; DM, diabetes mellitus.
* $p < 0.05$ between-groups comparison.

could increase the risk of type-I error due to the multiple statistical tests. However, since the Elixhauser comorbidity score was able to determine the patient's underlying disease from the national claims data, we used the Elixhauser comorbidity score in this study. Finally, as previously stated, the definition of hyperactive delirium used in our study has its limitations; Since, neuroleptics including haloperidol, risperidone, quetiapine could be used not only to treat hyperactive delirium but also as an adjuvant analgesic. Therefore, the incidence of the hyperactive delirium could have been overestimated. Also, the diagnosis of hyperactive delirium can be easily missed in a clinical setting, evaluating the nationwide claims data is difficult due to the variable incidence range. Thus, a working definition of

Table 3 Stepwise logistic regression.

	Odds Ratio	95% confidence interval	*p*-value
Age	4.723	4.151–5.375	<.0001*
Hospital type	0.075	0.042–0.132	<.0001*
ICU care	1.519	1.435–1.607	<.0001*
Sex	0.669	0.634–0.706	<.0001*
Depression	1.385	1.318–1.456	<.0001*
Neurodegenerative disorders	1.206	1.139–1.276	<.0001*
Psychosis	2.232	1.476–3.375	<.0001*
Diabetes, uncomplicated	1.093	1.041–1.148	0.0013*
Peptic ulcer disease, no bleeding	0.916	0.871–0.963	0.0006*
Ventilator care	1.193	1.013–1.404	0.0343*

ICU, intensive care unit.
* $p < 0.05$ between-group comparison.

hyperactive delirium is pertinent.[19] Further, delirium that does not require pharmacological intervention (such as the hypoactive subtype of delirium) may have been omitted in this study, so we must draw conclusions with caution.

Conclusion

We retrospectively analyzed data of nearly 6 million elderly patients who underwent surgery for hip fracture under regional anesthesia. Hyperactive delirium requiring pharmacologic intervention patients who underwent surgery for hip fracture under regional anesthesia was associated with multiple risk factors, including male sex, old age, preoperative neurodegenerative disorder, diabetes mellitus, peptic ulcer disease, psychosis, depression, ICU stay, and ventilator care.

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Ethical approval and consent to participate

The study was reviewed and approved by the institutional review board of Seoul Paik Hospital (IRB No 2019-05-005). The need to obtain informed consent was waived since we used de-identified administrative data.

Availability of data and material

Data cannot be shared publicly because of confidentiality and privacy issues. Data may be available with a formal application to the institutional ethics committee (contact via https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do) for researchers who meet the criteria for access to confidential data.

Conflicts of interest

The authors declare no conflicts of interest.

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