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Original Study

Use of Selective Serotonin Reuptake Inhibitors and Risk of Hip Fracture in the Elderly: A Case-Control Study in Taiwan

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A B S T R A C T

Background: This population based study investigated the relationship between use of selective serotonin reuptake inhibitors (SSRIs) and hip fractures in the elderly in Taiwan.
Methods: Analysis of a random sample of 1 million insurance enrollees' data identified 4,891 patients with newly diagnosed hip fractures and 4,891 controls without hip fracture between 2000 and 2011. Both cases and controls were ≥65 years of age and were matched by sex, age, comorbidities, and index year of hip fracture diagnosis. Patients were considered current SSRI users if their last SSRI tablet was taken ≤7 days before the hip fracture diagnosis. Late use of SSRIs was defined as taking the last SSRI tablet ≥8 days before the hip fracture diagnosis. Non-SSRI users comprised individuals who never had an SSRI prescription. Odds ratios (ORs) and 95% confidence intervals (CIs) for hip fracture associated with SSRI use was estimated by multivariate unconditional logistic regression.
Results: After adjustment for covariants, multivariate regression analysis showed that the adjusted OR of hip fracture was 2.17 for current SSRI users (95% CI: 1.60–2.93) compared with those who never used SSRIs. The adjusted OR was 1.11 for individuals with late use of SSRIs (95% CI: 0.96–1.28) and was not significant.
Conclusions: Current use of SSRIs was associated with a 2.17-fold increase in the odds of hip fracture in the elderly in Taiwan. Clinicians should consider the possibility of SSRI-associated hip fracture among old people currently taking SSRIs.

For the elderly, the incidence of hip fracture increases with age.[1] Even though the incidence of radius/ulna and spinal fractures increases with age, especially in women, the incidence of femur/hip fractures increases much more rapidly and steeply in men and women after 65 years of age.[1] Hip fractures not only injure the individual but are a family and socioeconomic burden, causing loss of productivity. In young adults, femoral fracture can result from severe trauma, such as a traffic accident or athletic injury. However, hip fractures can result from otherwise minor falls in people with decreased bone density caused by disease.

Even though there are ethnic differences in both hip fracture rate and decreased bone mineral density in the elderly,[2,3] the aging population is seen worldwide. A nationwide population study conducted in South Korea by Ha et al reported that the incidence of hip fracture increased by 14.1% in patients 50 years of age and older from 2008 to 2012.[4] In Taiwan, the incidence of hip fracture decreased from 317 per 100,000 person-years in 2004 to 211 per 100,000 person-years in 2011. However, the number of hip fractures is estimated to increase from 18,338 in 2010 to 50,421 in 2035 because of aging of the population.[5]

Extensive effort has been directed at increasing the safety of hip replacement surgery and reducing mortality,[6,7] but the comorbidities and first-year mortality rate after hip fracture remain high. The quality of life after hip fracture in the elderly is also a concern.[8] Therefore, decreasing the incidence of hip fracture in the elderly is of high importance.

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Age itself is a risk factor of hip fracture along with other unpreventable (eg, gender and ethnicity) and potentially preventable (eg, nutrition and medication) risk factors.[1,9,10] Several kinds of medication have been reported to be associated with hip fracture in the elderly. Corticosteroids increase the risk of hip fracture because of their widespread use in the elderly,[11] and the association of antidepressants with hip fractures is under investigation because of the prevalence of mental health problems and depression in the elderly. Concerns of multiple adverse effects of traditional tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in the elderly prompted development of selective serotonin reuptake inhibitors (SSRIs), which are frequently prescribed to treat depression in the elderly. Adverse effects have also been associated with SSRIs. In 1988, a case-control study conducted by Liu et al in Canada found that exposure to SSRIs, secondary-amine TCAs, and tertiary-amine TCAs may increase the risk of hip fracture in elderly people.[12] Since then, several other SSRIs have been approved, and the association between SSRIs and hip fractures is ongoing.[13] Most studies have been conducted in Western countries; few were conducted in Asia. We conducted this population-based case-control study to investigate the association between SSRI use and the risk of hip fracture in the elderly in Taiwan.

Methods

Data Source

Of Taiwan's 23 million residents, 99% are covered by the National Health Insurance (NHI) program, which contracts with more than 97% of healthcare institutions.[14] The data in this case-control study were retrieved from the Taiwan Longitudinal Health Insurance Database 2000 (LHID 2000). Data were randomly selected from the medical claims records of all NHI 2000 Registry of Beneficiary enrollees. To protect personal information, patient data were encrypted before the LHID 2000 was released for public use. The details of the program can be found in previous high-quality study.[15] This study was approved by the Institutional Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Sampled Participants

We identified individuals ≥65 years of age with hip fractures (ICD-9-CM code 820) from LHID 2000 during the years 2000 to 2011. The diagnosis date of hip fracture was recorded as the index date. Control subjects without a diagnosis of hip fracture were also identified in the LHID 2000. The hip fracture and control patients were selected using a 1:1 ratio of propensity score matching.[16] We used a logistic regression model to calculate the propensity scores. The potential confounders included sex, age, the year of hip fracture diagnosis, and comorbidities, including alcohol-related disease (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0–571.3, 790.3, and V11.3), cardiovascular disease (ICD-9-CM codes 410–414, 428, 430–438, and 440–448), chronic kidney disease (ICD-9-CM codes 585–586, and 588.8–588.9), chronic obstructive pulmonary diseases (ICD-9-CM codes 491, 492, 493, 496), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM codes 272.0, 272.1, 272.2, 272.3, and 272.4), hypertension (ICD-9-CM codes 401–405), and osteoporosis (ICD-9-CM code 733). The diagnostic accuracy of comorbidities based on ICD-9 codes has been confirmed in previous studies.[17,18]

Measurements of SSRI Use and Non-SSRI Antidepressant Use

Individuals classified as having current use of SSRIs included those whose last remaining tablet of SSRIs was taken ≤7 days before the hip fracture diagnosis or those having SSRIs tablets at that time. Individuals whose last remaining SSRI tablet was taken ≥8 days before the date of hip fracture were classified as late use of SSRIs. Individuals who never had an SSRI prescription were classified as never used SSRIs. We also conducted an analysis on the dose-dependent effect among those currently using SSRIs. The average daily SSRI dose was calculated by dividing the total number of SSRIs by the total number of days the tablets were taken. The average daily dose was divided into 2 levels by the median dose. Medication history of non-SSRI antidepressant use was also recorded for each patient.

Statistical Analysis

We first compared the demographic characteristics, that is, percentages of participants, by SSRI use, non-SSRI use, and comorbidities in patients with hip fractures and controls using the χ^2 test for categorical variables. Student *t* test was used to test the difference of mean ages between the cases and controls. Univariate and multivariate unconditional logistic regression analyses were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between SSRI use and hip fracture. A multivariable analysis was conducted adjusting for non-SSRI use and alcohol-related diseases. An additional analysis of the dose-dependent effect was conducted among those currently using SSRIs. The average daily SSRI dose was calculated by dividing using the total number of SSRI doses by the total number of days the drug was taken. For analysis of dose-dependency, the average daily dose was divided into 2 levels by the median dose, that is, <20 mg and ≥20 mg. All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Cary, NC), and the results were considered statistically significant when the 2-tailed *P* values were <.05.

Results

Descriptive Characteristics of the Study Population

We identified 4891 new cases of hip fracture and 4891 controls without hip fracture from a database of 1 million randomly selected insurance claims made from 2000 to 2011 (Table 1). Cases and controls were sex- and age-matched. The mean ages (standard deviations) of 79.0 (7.0) years in cases and 78.8 (6.9) years in controls were not significantly different (*t* test, $P = .12$). The proportions of cases with current and late use of SSRIs were significantly greater than in controls (2.9% vs 1.1%, and 9.4% vs 8.3%, respectively; χ^2 test, $P < .001$). Similarly, the proportion of cases that had ever used non-SSRI antidepressants was higher in cases than in controls (χ^2 test, $P < .001$). The proportion of controls with alcohol-related diseases was higher than that in cases (χ^2 test, $P = .01$). There were no significant differences in the proportions of cases and control participants with other comorbidities (χ^2 test, $P > .05$).

Risk of Hip Fracture Associated With SSRI Use

After adjustment for covariants, the multivariable logistic regression analysis showed that the adjusted OR of hip fracture was 2.17 for individuals with current use of SSRIs (95% CI 1.60–2.93), when compared with individuals who never used SSRIs. The adjusted OR was 1.11 for individuals with late use of SSRIs (95% CI 0.96–1.28), which was not significant (Table 2). Use of non-SSRI antidepressants was associated with hip fracture (adjusted OR 1.22, 95% CI 1.12–1.33).

Risk of Hip Fracture Associated With Average Daily Dose of Current Use of SSRIs

We conducted an analysis of the dose-dependent effect among those with current use of SSRIs. The average daily SSRI dose was determined by dividing the total prescribed dose by the total number