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Original article

Association between medication use and peri-operative delirium in older adult patients with hip fracture at King Chulalongkorn Memorial Hospital

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Background: Delirium is a common adverse consequence in the hip fracture population. Many medications can affect the emergence of the perioperative delirium but the data of older patients with hip fracture is lacking.
Objective: To investigate the association between the type and the number of medications and the occurrence of perioperative delirium in older patients with hip fracture.
Methods: This is a cross-sectional study which collected data from patients aged ≥ 65 years who underwent hip surgery at King Chulalongkorn Memorial Hospital. The Delirium Rating Scale-Revised-98-Thai version (DRS - R -98-T) was used to assess the delirium one day before the surgery, and the second day and the forth day after the surgery. Unpaired *t* - test, Pearson's Chi-square test, and linear regression model were used to determine the association between different clinical variables.
Results: Forty patients (33.3%) of 120 older patients with hip fracture developed delirium during their hospital stay. Regarding the association between pre - operative medications and pre-operative delirium in linear regression model; benzodiazepine decreased DRS-R-98-T score ($P = 0.004$), beta-blocker decreased DRS-R-98-T score ($P = 0.038$), while antibiotic exposure increased DRS-R-98-T score ($P = 0.035$). Post-operative delirium was directly associated with exposure to antipsychotic drugs (pre- and post-operative use) ($P = 0.045$ and < 0.001 respectively) but inversely associated with benzodiazepines (pre - and post - operative use) ($P = 0.04$ and 0.024, respectively) and inversely associated with anticonvulsants (post-operative use) ($P < 0.001$). Age, dementia, gastrointestinal diseases, body mass index, history of life-time delirium, use of restraints, and history of blood transfusion were associated with increased DRS-R-98-T score.
Conclusion: Antibiotic exposure was associated with increased preoperative delirium, while benzodiazepines and beta blocker were associated with decreased preoperative delirium in older adults with hip fracture. Benzodiazepines and anticonvulsants might be inversely associated with postoperative delirium. The peri-operative delirium was not associated with the number of pre-hospital medications. These medications are modifiable factors for delirium prevention, so they should be cautiously used in older patients with hip fracture.

Keywords: Delirium, hip fracture, medication.

Hip fracture is a prevalent and debilitating medical condition in older people. It was globally estimated that hip fractures affected around 18.0% of women and 6.0% of men. [1, 2] It decreases daily activity performance [1] and increases 1 - year mortality rate up to 40.0%.[3] Orthopedic surgery is the treatment of choice for hip fracture as it enhances early mobilization and reduces the 2-year mortality rate compared to non-operative treatment. [4] Delirium is a common adverse consequence after hip fracture. It is clinically described as an acute alteration of consciousness, impaired attention, and global cognitive disturbance. [5, 6] Delirium occurs in 13 to 55.9% of older patients with hip fracture. [7]

Certain medications are identified as the major precipitating factors of delirium, including benzodiazepines and high-potency anticholinergic drugs. [8] Prior studies show that pre-operative psychoactive medication use increased the rate of post-operative delirium up to 2 - 7 times, and pre-operative narcotic medication use increased

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post-operative delirium up to 3 times. Cardiovascular agents were also reported to be associated with delirium. Unsurprisingly, polypharmacy was another contributory factor to post-operative delirium. [9]

Our group recently reported the pre- and post-operative delirium prevalence in older hip fracture adult patients to be 23.0% and 16.4%, respectively. [10, 11] Factors associated with delirium included aging, a previous delirium history, dementia history, waiting time to surgery more than 48 hours, and lower cognitive performance measured by the Thai Mental Status Examination. We also found that peri-operative delirium in hip fracture patients was associated with immune-inflammatory pathway disturbance involving activated immune-inflammatory pathways and reduced negative immune-regulatory pathways. [12] The information regarding medication exposure and the delirium development in older hip fracture patients in Thailand has not been explored yet.

Many medications could affect the emergence of perioperative delirium but data of this issue in the elderly hip fracture population is lacking. Therefore, we hypothesized that certain medications the patients received before or after their hip fracture operation are associated with delirium syndrome during the hospital stay. This study aimed to investigate the association between the type and the number of medications and delirium occurrence in older patients with hip fracture.

Materials and methods

This was a cross - sectional descriptive study aiming to investigate the association between the type and the number of medications and delirium occurrence in older patients with hip fracture. It was conducted between June 2021 to August 2022 at King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand. The study has been approved by the Human Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University (IRB no. 382/64).

Population and sample

The study population was older adult patients who were admitted to the orthopedic or trauma surgery units at KCMH. The inclusion criteria for this study were patients aged ≥ 65 years who suffered from hip fracture and underwent hip fracture surgery who were able to understand and communicate in Thai. The patients and/or their surrogate decision makers gave their consent to participate in the study. The exclusion criteria were patients who received nonsurgical hip fracture treatment, or who were unable to communicate with the researchers due to serious/ emerging medical conditions (for example: intubation, pulmonary embolism, myocardial infarction), had severe auditory or visual impairment, suffered from a high - energy impact hip fracture, suffered from a pathologic hip fracture due to metastatic illness, or had concurrent traumatic head injury. We used the method described by Lwanga SK. and Lemeshow S. [13] to estimate the sample size. The calculated sample size for this study was 117 subjects.

Data collection

The orthopedic physicians notified the consultation psychiatry research team of any patients admitted into the hip fracture care pathway. After the electronic medical record data screening, the research team visited the patient who met the research criteria within 24 hours before surgery to request informed consent regarding their participation in the study. The study subjects would later be interviewed by the research psychiatrist or psychiatry residents using the research questionnaire and delirium screening tools. We also collected data from the patient's relatives, nursing staff, and medical records which took approximately 15 - 30 minutes. Delirium information was not collected on the surgical date (day 1) as most of the patients would be monitored in the intensive care unit and most of them were postoperatively sedated. The research team would reassess the patient again on days 2 and 4 after the surgery (Figure 1). The evaluation period on those days was between 3 - 6 p.m. in June 2021 - August 2022.

Measurements

The primary independent variables were the type of medication used in the hospital before the delirium event and the number of perioperative medication exposure. Additionally, secondary independent variables were general demographic information (e.g., age, gender, marital status) and other clinical information before and after surgery. This clinical information included body mass index (BMI), underlying disease, past history of delirium, substance history, waiting time for surgery, cognitive function, pain score, use of restraints, and estimated blood loss during surgery. As for the baseline evaluation of cognitive function, we used the Thai Mental State Examination (TMSE), which is a standard bedside cognitive evaluation test commonly used in Thailand. A cutoff score of ≤ 23 indicates dementia. [14, 15]

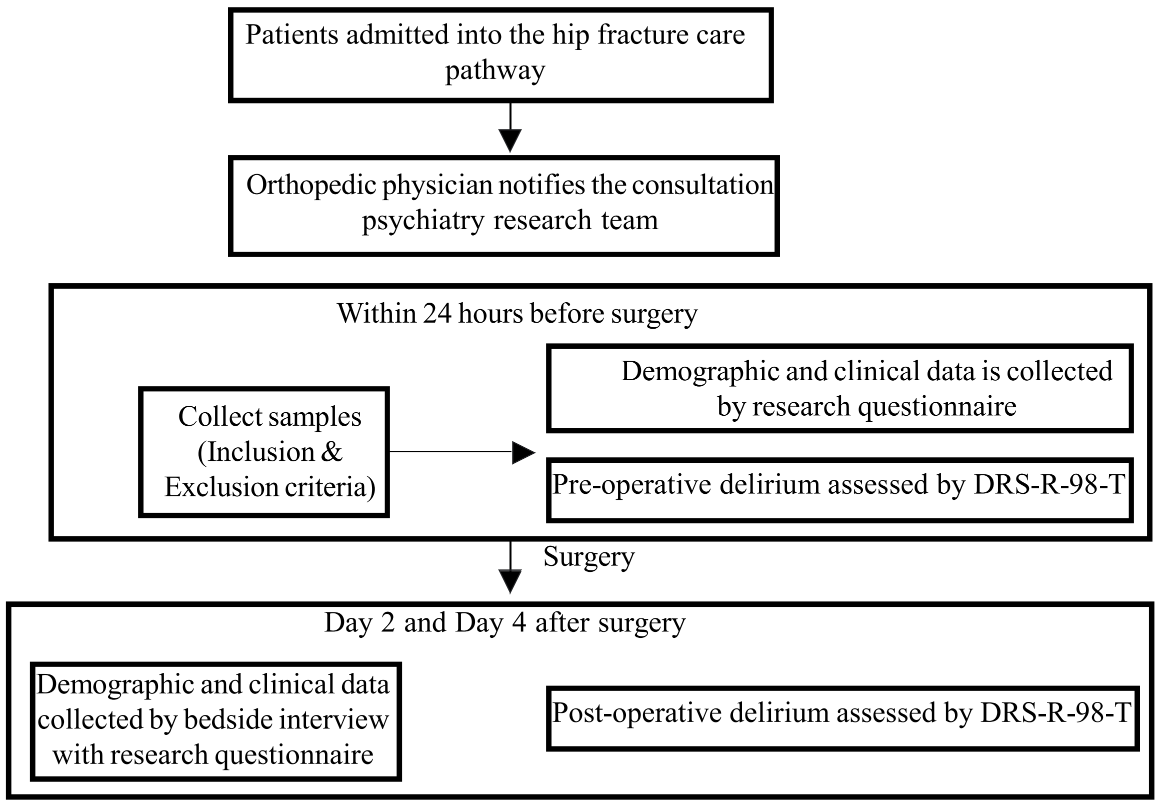

Figure 1. Study flow chart.

Outcome measurement

The primary outcome of this study was preoperative and post-operative delirium. Delirium Rating Scale-Revised 98-Thai version (DRS-R-98-T) was used to assess delirium one day before, and 2 and 4 days after surgery.[16, 17] As for the evaluation of DRS-R-98-T in post-operative delirium, we chose only one day (2 or 4 days after surgery) which had the maximal DRS-R-98-T score. The DRS-R-98-T includes two sections: three diagnostic items for initial ratings and a 13-item severity scale. Items covered language, thought processes, motor presentations, and five components of cognition. The cutoff value for delirium diagnosis is 15. The Cronbach's alpha coefficient in the delirium group was 0.90 for the DRS-R-98 total scale.[16]

Statistical analysis

Frequency and percentages were used to describe categorical variables such as gender, marital status, underlying disease, and medication use. Means with standard deviation were used to represent continuous variables such as age and duration of preoperative stays.

We used unpaired *t* - test to compare the mean difference of outcome variable between two categorical groups such as age and duration of preoperative hospital stay. We used Pearson's Chi - square test to compare categorical variables (e.g., gender, underlying disease) between the two groups. Finally, linear regression was used to show the association between medication use and delirium. The statistical significance was set at a *P* - value less than 0.05. All statistical analyses were performed using SPSS version 28.0.

Results

A total of 120 older patients who underwent hip fracture surgery consented to participate in this study. Using DRS-R-98-T, 40 patients (33.3%) developed delirium during the hospital stay. Preoperatively, delirium was present in 25 patients (20.8%). Most patients with preoperative delirium continued to be symptomatic in the postoperative period as well (21 patients). Fewer patients (15 patients) developed delirium only in the postoperative period. The most common subtype of delirium was hypoactive, followed by hyperactive and mixed subtypes, respectively (Figure 2).

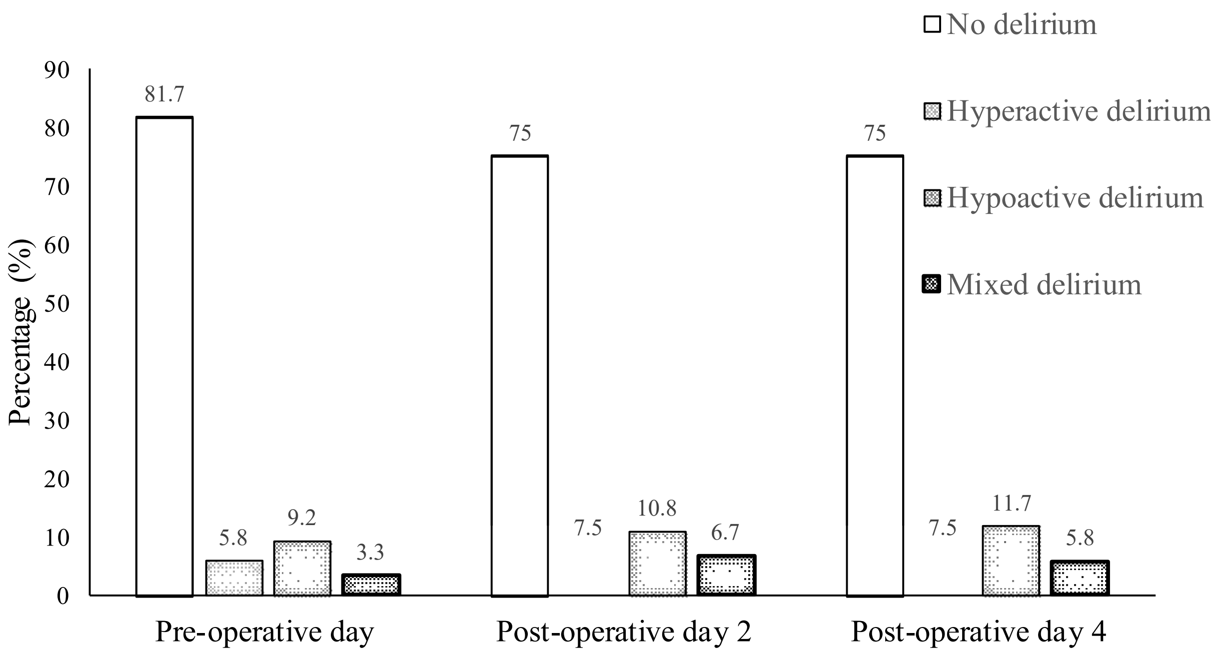

Figure 2. Demonstrated delirium in pre-operative and post-operative day.

Table 1 shows baseline demographic and clinical data. Most subjects were female (79.2%). The mean age in the delirium group was 85.2 years, which is statistically higher than the mean age of the non - delirium group (78.3 years). Delirious hip fracture patients were found to have significantly lower BMI (P = 0.008), they were more likely to have hearing impairment (P = 0.001), history of dementia (P < 0.001), underlying gastrointestinal disease (P = 0.028), lifetime delirium (P = 0.003), restraint (P < 0.001), blood transfusion in hospital (P < 0.001), and decreased mean TMSE score (P < 0.001). In contrast, the number of underlying diseases and the number of prehospital medications were not significantly different between the two groups. The prevalence of most underlying diseases were also not significantly different.

Table 2 shows the association between preoperative medications and preoperative delirium. Subjects using benzodiazepines had significantly less DRS-R-98-T mean score than patients who did not use benzodiazepines (P = 0.002, mean difference - 4.437, 95% CI - 7.536 to - 1.339). Subjects using anticonvulsants had also significantly less DRS-R-98-T mean score (P < 0.001, mean difference - 5.409, 95% CI - 7.650 to - 3.168), whereas subjects using antipsychotic drugs had higher mean score (P = 0.01, mean difference 7.550, 95% CI 2.012 to 13.088). In addition, subjects using calcium channel blockers had a higher DRS-R-98-T score but the number did not reach the statistical significance (P = 0.063, mean difference 2.836, 95% CI - 0.160 to 5.832).

Table 3 presents the result of linear regression analysis of preoperative delirium scores after controlling for confounding factors (age, BMI, hearing impairment, dementia, gastrointestinal disorder, history of life-time delirium). Receiving benzodiazepines before the operation was associated with a decreased DRS-R-98-T score (P = 0.004). Receiving beta-blockers also decreased DRS-R-98-T score (P = 0.038). In contrast, receiving antibiotics was associated with an increased DRS-R-98-T score (P = 0.035). Using antipsychotic drugs and anticonvulsants did not change the DRS-R-98-T score in this model. In addition, age, dementia, gastrointestinal diseases, and lifetime history of delirium were statistically correlated with an increased DRS-R-98-T score (P < 0.001).

Table 4 shows the association between preoperative medication exposure and postoperative delirium. The findings show that subjects using benzodiazepines had significantly less DRS-R-98-T score (P = 0.04, mean difference - 3.900, 95% CI - 7.622 to - 0.178), whereas subjects using antipsychotic drugs had more DRS-R-98-T score (P = 0.045, mean difference 6.210, 95% CI 0.151 to 12.269).

Table 5 demonstrates the association between postoperative medication exposure and postoperative delirium. Again, subjects using benzodiazepines or anticonvulsants after hip-fracture surgery had significantly less DRS-R-98-T score with a $P = 0.024$ and < 0.001 respectively. On the contrary, the subjects who were exposed to antipsychotic drugs after surgery had higher DRS-R-98-T scores ($P < 0.001$, mean difference 10.300, 95% CI 6.457 to 14.143).

By using the linear regression model in Table 6, we found no association between preoperative/ postoperative medication exposure and postoperative delirium. However, age, dementia, gastrointestinal diseases, BMI, lifetime history of delirium, restraint, and blood transfusion were all associated with an increased DRS-R-98-T score.

Table 1. Demographic and clinical data comparing between patients with and without delirium during admission for hip-fracture surgery in KCMH.

	Total = 120 (n, %)	**Delirium = 40 (n, %)**	**Non – delirium = 80 (n, %)**	***P* – value**	**X^2**
Gender				0.525	0.404
Male	25 (20.8)	7 (17.5)	18 (22.5)		
Female	95 (79.2)	33 (82.5)	62 (77.5)		
Marital status				0.518	0.417
Couple	62 (51.7)	19 (47.5)	43 (53.8)		
Non-couple (single, widow, divorce)	58 (48.3)	21 (52.5)	37 (46.3)		
Body mass index (BMI)				0.008*	6.995
BMI < 23 kg/m^2	73 (60.8)	31 (77.5)	42 (52.5)		
BMI ≥ 23 kg/m^2	47 (39.2)	9 (22.5)	38 (47.5)		
Sensory impairment					
Visual impairment	6 (5.0)	3 (7.5)	3 (3.8)	0.374	0.789
Hearing impairment	10 (8.3)	8 (20.0)	2 (2.5)	0.001*	10.691
Underlying disease					
Neurological					
- Dementia	23 (19.2)	18 (45.0)	5 (6.3)	0.001*	25.845
- Non-dementia	28 (23.3)	8 (20.0)	20 (25.0)	0.542	0.373
Psychiatric	16 (13.3)	6 (15.0)	10 (12.5)	0.704	0.144
Cardiovascular	96 (80)	34 (85.0)	62 (77.5)	0.333	0.938
Respiratory	8 (6.7)	4 (10.0)	4 (5.0)	0.301	1.071
Gastrointestinal	7 (5.8)	5 (12.5)	2 (2.5)	< 0.028*	4.855
KUB[a]	22 (18.3)	7 (17.5)	15 (18.8)	0.868	0.028
Endocrine	76 (63.3)	26 (65.0)	50 (62.5)	0.789	0.072
Hematologic	4 (3.3)	2 (5.0)	2 (2.5)	0.472	0.517
Orthopedic	11 (9.2)	5 (12.5)	6 (7.5)	0.371	0.801
Others	3 (2.5)	2 (5.0)	1 (1.3)	0.215	1.538
Lifetime history of delirium	19 (15.8)	12 (30.0)	7 (8.8)	0.003*	9.036
Family history of psychiatric disorder	6 (5.0)	3 (7.5)	3 (3.8)	0.374	0.789
History of substance use					
Alcohol use	3 (2.5)	0 (0.0)	3 (3.8)	0.550[b]	
Nicotine use	2 (1.7)	0 (0.0)	2 (2.5)	0.552[b]	
Restraint in hospital	17 (14.2)	15 (37.5)	2 (2.5)	< 0.001*	26.865
Blood transfusion in hospital	69 (57.5)	32 (80.0)	37 (46.3)	< 0.001*	12.430
Age (year)	80.6 (7.7)	85.2 (5.2)	78.3 (7.7)	< 0.001*	6.888 (4.546, 9.229)
Number of underlying diseases	3.0 (1.7)	3.4 (1.9)	2.8 (1.6)	0.082	0.575 (-0.075, 1.225)
Number of pre-hospital medication	6.8 (5.04)	7.0 (4.5)	6.7 (5.3)	0.799	0.250 (-1.692, 2.192)
Length of hospital stay before surgery (hour)	87.8 (111.3)	94.2 (99.0)	84.6 (117.5)	0.659	9.575 (-33.270, 52.420)
TMSE score (baseline)	20.46 (7.7)	13.23 (8.4)	24.1 (3.7)	< 0.001*	-10.850 (-13.692, -8.048)

[a]kidney and urinary bladder system, [b]Fisher's Exact Test
*$P < 0.05$

Table 2. The distribution and relationship between preoperative medications and preoperative delirium.

	Total (n, %)	**DRS-R-98 score in medication exposure group [mean, SD]**	**DRS-R-98 score in medication non-exposure group [mean, SD]**	***P*– value**	**Mean difference**	**95% CI**
Benzodiazepine	40 (33.3)	6.1 (5.9)	10.5 (8.9)	0.002*	- 4.437	- 7.536, -1.339
Opiate/narcotics	57 (47.5)	7.9 (7.9)	10.1 (8.5)	0.146	- 2.216	- 5.213, 0.780
Anticholinergic	22 (18.3)	7.8 (6.9)	9.3 (8.6)	0.425	- 1.574	- 5.465, 2.317
Antihistamine	10 (8.3)	9.4 (7.7)	9.0 (8.3)	0.893	0.373	- 5.089, 5.835
Antipsychotic	20 (16.7)	15.3 (11.5)	7.8 (6.9)	0.010*	7.550	2.012, 13.088
Antidepressant	14 (11.7)	10.8 (10.8)	8.8 (7.9)	0.411	1.956	- 2.734, 6.645
Anticonvulsant	10 (8.3)	4.1 (2.3)	9.5 (8.5)	< 0.001*	- 5.409	- 7.650, -3.168
Corticosteroid	3 (2.5)	8.7 (8.9)	9.1 (8.3)	0.935	- 0.402	- 10.072, 9.268
Antiparkinsonian agents	5 (4.2)	7.6 (1.8)	9.1 (8.4)	0.200	- 1.522	- 3.943, 0.899
Cardiovascular agents	25 (20.8)	9.5 (9.4)	8.9 (8.0)	0.757	0.583	- 3.133, 4.299
BB [a]	53 (44.2)	10.6 (8.5)	7.8 (7.9)	0.063	2.836	- 0.160, 5.832
CCB [b]	34 (28.3)	8.3 (6.0)	9.4 (9.0)	0.456	- 1.066	- 3.898, 1.765
ACEI / ARB [c] Diuretics	21 (17.5)	11.1 (11.0)	18.6 (7.5)	0.329	2.527	- 2.710, 7.764
Bronchodilator	4 (3.3)	12.0 (6.4)	8.9 (8.3)	0.474	3.043	- 5.349, 11.435
Antibiotic	11 (9.2)	12.3 (10.7)	8.7 (8.0)	0.180	3.539	- 1.653, 8.731

[a]Beta blockers, [b]Calcium channel blockers
[c]Angiotensin converting enzyme inhibitor / Angiotensin receptor blockers
*$P < 0.05$

Table 3. Linear regression model of the associations between preoperative delirium and other clinical factors[a].

	Unstandardized B	**Coefficients standard error**	***t***	***P* – value**	**95% CI**
(Constant)	- 18.358	5.353	- 3.430	< 0.001	- 28.964, - 7.752
Dementia	8.769	1.333	6.580	< 0.001	6.128, 11.409
Gastrointestinal diseases	11.402	2.148	6.589	< 0.001	7.145, 15.658
Aging	0.317	0.066	4.784	< 0.001	0.186, 0.448
History of life-time delirium	4.922	1.439	3.420	< 0.001	2.070, 7.773
Pre-operative medication (benzodiazepines)	- 3.086	1.052	- 2.935	0.004	- 5.170, - 1.003
Pre-operative medication (antibiotic drugs)	3.648	1.714	2.129	0.035	0.253, 7.044
Pre-operative medication (beta-blocker drug)	- 2.646	1.261	- 2.098	0.038	- 5.144, 0.147

[a] Included covariates: age, BMI, hearing impairment, dementia, gastrointestinal disorder, history of life-time delirium, pre-operative medication, adjusted R square 0.585

Table 4. The distribution and relationship between preoperative medication exposure and postoperative delirium.

	Total (n, %)	DRS-R-98 score in medication exposure group [mean, SD]	DRS-R-98 score in the medication non-exposure group [mean, SD]	*P* – value	Mean difference	95% CI
Benzodiazepine	40 (33.3)	8.8 (8.5)	12.7 (10.2)	0.040*	- 3.900	- 7.622, -0.178
Opiate/narcotics	57 (47.5)	11.0 (10.2)	10.8 (9.6)	0.695	- 0.709	- 4.284, 2.865
Anticholinergic	22 (18.3)	9.9 (7.5)	11.8 (10.3)	0.399	- 1.968	- 6.570, 2.634
Antihistamine	10 (8.3)	9.8 (6.10)	11.6 (10.1)	0.588	- 1.773	-8.227, 4.682
Antipsychotic	20 (16.7)	16.6 (12.5)	10.4 (8.9)	0.045*	6.210	0.151, 12.269
Antidepressant	14 (11.7)	13.6 (12.6)	11.1 (9.4)	0.372	2.511	- 3.034, 8.056
Anticonvulsant	10 (8.3)	6.9 (6.3)	11.8 (10.0)	0.129	- 4.936	- 11.336, 1.463
Corticosteroid	3 (2.5)	9.3 (11.0)	11.5 (9.8)	0.711	- 2.145	- 13.579, 9.288
Antiparkinsonian agents	5 (4.2%)	9.6 (5.2)	11.5 (9.9)	0.674	- 1.904	- 10.836, 7.027
Cardiovascular agents						
BB [a]	25 (20.8)	12.8 (10.1)	11.0 (9.8)	0.435	1.735	- 2.650, 6.123
CCB [b]	53 (44.2)	12.7 (10.2)	10.4 (9.5)	0.202	2.314	- 1.258, 5.886
ACEI / ARB [c]	34 (28.3)	10.5 (9.4)	11.9 (10.0)	0.533	- 1.250	- 5.207, 2.707
Diuretics	21 (17.5)	12.9 (12.9)	11.1 (9.1)	0.537	1.851	- 4.242, 7.945
Bronchodilator	4 (3.3)	15.7 (6.9)	11.3 (9.9)	0.373	4.474	- 5.443, 14.391
Antibiotic	11 (9.2)	13.4 (10.7)	11.2 (9.8)	0.475	2.234	- 3.942, 8.411

[a]Beta blockers, [b]Calcium channel blockers
[c]Angiotensin converting enzyme inhibitor / Angiotensin receptor blockers
*$P < 0.05$

Table 5. The distribution and relationship between post-operative medication and post-operative delirium.

	Total (n, %)	DRS-R-98 score in medication exposure group [mean, SD]	DRS-R-98 score in medication non-exposure group [mean, SD]	*P* – value	Mean difference	95% CI
Benzodiazepine	16 (13.3)	7.0 (7.5)	12.1 (10.0)	0.024*	- 5.106	- 9.486, - 0.726
Opiate/narcotics	90 (75.0)	11.1 (10.1)	9.8 (8.9)	0.288	2.211	- 1.894, 6.316
Anticholinergic	62 (51.7)	10.8 (9.5)	12.1 (10.2)	0.445	- 1.380	- 4.945, 2.185
Antihistamine	9 (7.5)	11.0 (12.3)	11.5 (9.7)	0.893	- 0.459	- 7.240, 6.321
Antipsychotic	27 (22.5)	19.4 (9.8)	9.1 (8.6)	< 0.001*	10.300	6.457, 14.143
Antidepressant	12 (10.0)	16.6 (14.9)	10.9 (9.0)	0.216	5.731	- 3.831, 15.294
Anticonvulsant	16 (13.3)	5.8 (4.5)	12.3 (10.1)	< 0.001*	- 6.476	- 9 .525, - 3.427
Corticosteroid	3 (2.5)	10.3 (7.4)	11.4 (9.9)	0.847	- 1.120	- 12.558, 10.319
Antiparkinsonian agents	6 (5.0)	10.7 (4.0)	11.4 (10.0)	0.684	- 0.798	- 5.107, 3.510
Cardiovascular agents						
BB [a]	21 (17.5)	12.8 (9.9)	11.1 (9.8)	0.480	1.678	- 3.013, 6.369
CCB [b]	57 (47.5)	11.4 (9.2)	11.5 (10.4)	0.967	- 0.074	- 3.651, 3.502
ACEI / ARB [c]	25 (20.8)	12.3 (10.3)	11.2 (9.8)	0.627	1.080	- 3.314, 5.474
Diuretics	23 (19.2)	11.4 (9.8)	11.4 (9.9)	0.986	- 0.042	- 4.579, 4.496
Bronchodilator	3 (2.5)	10.0 (7.8)	11.5 (9.9)	0.801	- 1.462	- 12.899, 9.976
Antibiotic	71 (59.2)	10.5 (9.5)	12.7 (10.3)	0.235	- 2.179	- 5.791, 1.433

[a]Beta blockers, [b]Calcium channel blockers
[c]Angiotensin converting enzyme inhibitor / Angiotensin receptor blockers
*$P < 0.05$

Table 6. Linear regression model showed the associations between post-operative delirium and other clinical factors[a].

	Unstandardized B	**Coefficients standard error**	***t***	***P* – value**	**95% CI**
(Constant)	-20.100		-2.993	<0.003	-33.406, -6.794
Aging	0.299	0.085	3.503	<0.001	0.130, 0.468
Dementia	6.834	1.749	3.907	<0.001	3.369, 10.300
Gastrointestinal diseases	8.365	2.638	3.171	0.002	3.138, 13.592
Body mass index > 23 kg/m^2	3.025	1.260	2.401	0.018	0.528, 5.521
Lifetime history of delirium	3.616	1.743	2.075	0.040	0.163, 7.069
Restraint	6.676	2.000	3.337	0.001	2.713, 10.639
Blood transfusion in hospital	3.963	1.283	3.088	0.003	1.420, 6.506

[a]Include covariate factors (age, body mass index, hearing impairment, dementia, gastrointestinal disorder, history of lifetime delirium, pre-operative medication, post-operative medication, restrain, blood transfusion), adjusted R square 0.560

Discussion

The primary aim of this study was to explore the association between medication use and pre- and postoperative delirium in older hip fracture patients. We found that preoperative hip fracture delirium was associated with exposure to antibiotics and inversely associated with exposure to benzodiazepines and beta - blockers. We found that postoperative delirium was associated with exposure to antipsychotic drugs (both pre- and post - operative use), but inversely associated with benzodiazepines (pre - and postoperative use) and anticonvulsants (postoperative use). In the linear regression model, we did not find a significant association between postoperative delirium and any medication class when controlling for other covariate factors. We did not find a significant association between the number of pre - hospital medications and peri - operative delirium in this study. In addition, other factors associated with pre- or postoperative delirium were aging, dementia, gastrointestinal diseases, and lifetime history of delirium.

From previous studies [8, 9], benzodiazepines increased delirium incidence 1.16 - 3.08 times, which was opposite to the findings from our study. The first explanation for this contradictory result is that exposure to a low dose of benzodiazepines may benefit sleep; thus, it may lower the sleep - wake cycle disturbance item of the DRS-R-98-T. Moreover, the study of Burry LD, *et al*.[8] discussed an inconsistent correlation between benzodiazepine exposure and delirium as well as the low likelihood of delirium development with low dose benzodiazepine use which is concordant to our findings. Some patients in our study were long - term benzodiazepine users, hence continuing this medication during the admission may have prevented benzodiazepine withdrawal. [18] Two prior studies [19, 20] also supported that combining benzodiazepine (lorazepam) with antipsychotic drug (haloperidol) might benefit in delirium management in terminally ill patients. Our study also indicated that preoperative beta blocker exposure also decreased preoperative delirium. The explanation of this finding is supported by the review of delirium pathophysiology in 2017 [21] which described an association between delirium in traumatic injury or operative patients and increased norepinephrine level. Beta blockers such as propranolol may lower the level of sympathetic activity and hypertensive stress upon the central nervous system, which was protective in our patients. Although some other studies [9, 22] reported opposite findings in which preoperative beta blocker exposure increased postoperative delirium in vascular surgery settings. Different clinical conditions, type of operations, as well as delirium assessment time frame may contribute to these inconsistent findings. Therefore, more studies regarding the association between beta blockers and perioperative delirium in orthopedic settings are required.

Anticonvulsants decreased preoperative delirium in the primary statistical analysis, although it did not reach a significant level in the linear regression model. Leung JM, *et al*. reported a postoperative delirium rate reduction in a randomized pilot trial comparing between gabapentin and placebo.[23] We also found that preoperative antibiotic exposure was associated with increased preoperative delirium. This finding may be confounded by the fact that delirium is caused by systemic infection and inflammation requiring antibiotic usage.[24] In addition, the study of Teng C, *et al.* [25] reported that antibiotics such as ciprofloxacin, ceftazidime, and metronidazole were associated with a delirium incidence. Unsurprisingly, antipsychotics were found to be associated with pre- and postoperative delirium, but they did not reach a statistical significance after controlling covariates. Antipsychotic use in our study was likely a consequence of delirium diagnosis as this medication class is the first line agent for delirium management. [26]

Beside benzodiazepines, anticonvulsants, and antibiotics, we found no additional association between other medication classes and postoperative delirium. The duration of any medication exposure in this study might not be prolonged enough to induce delirium as our hip fracture program attempted to shorten the waiting time to surgery and length of stay during the study period. Therefore, medication exposure in this study might impact the perioperative delirium occurrence less than other factors. Narcotic and anticholinergic medications were not associated with pre or postoperative delirium in this study, which is similar to some previous studies. [8, 27] Adequate amounts of opioid medication is crucial in perioperative pain control and delirium prevention. Morrison RS, *et al.* reported that too low or too high equivalent doses of opioids can contribute to delirium in the hip fracture population. [28] The anticholinergic agents commonly used in this study were orphenadrine. Their anticholinergic loading risk may not be as high as other anticholinergic agents such as benztropine or amitriptyline, and therefore may have not led to a statistically or clinically significant effect. [29]

There are several limitations in this study, however. First, the sample size may not be large enough to explore the association between delirium in hip fracture and some medication classes. Second, this is a cross - sectional study which is able to demonstrate only the correlation between medication use and delirium, but not able to show the causality. Thirdly, we did not include intraoperative medications into the study's analysis. There were reports of an adverse association between some anesthetic agents such as midazolam or propofol and the delirium syndrome. [30, 31] Lastly, several clinical factors were not included in this study such as a medication dosage, fluid and albumin status, drug level, or pain score during the admission.

Conclusion

Antibiotic exposure was associated with increased preoperative delirium, while benzodiazepines and beta blocker were associated with decreased preoperative delirium in older adults with hip fracture. Benzodiazepines and anticonvulsants might be inversely associated with postoperative delirium. The peri-operative delirium was not associated with the number of pre-hospital medications. These medications were one of the potentially modifiable precipitating or protective factors for delirium prevention. Therefore, some medication classes should be judiciously used in the delirium-prone older patients with hip fracture. Future research is needed to further elucidate the causative effect of each medication class, its dosage, and duration of exposure to the emergence of delirium.

Conflicts of interest statement

The authors have each completed an ICMJE disclosure form. None of the authors declare any potential or actual relationship, activity, or interest related to the content of this article.

Data sharing statement

The present review is based on the references cited. Further details, opinions, and interpretation are available from the corresponding authors on reasonable request.

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