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Difference in Mortality Rate by Type of Anticoagulant in Elderly Patients with Cardiovascular Disease after Hip Fractures

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Background: The purpose of this study was to investigate the difference in mortalilty rate between cardiovascular disease (CVD) patients and non-CVD patients after hip fracture surgery performed in elderly patients. In addition, we compared the effect of CVD medication on mortality after hip fracture surgery.

Methods: Patients who underwent surgery for femoral intertrochanteric or neck fracture from January 2003 to December 2013 were enrolled in this study. After applying exclusion criteria, we categorized patients into group I (833 patients, non-CVD group) and group II (811 patients, CVD group). The CVD group was subcategorized as group IIa (332 patients, no medication), group IIb (381 patients, antiplatelet agents), and group IIc (98 patients, anticoagulation agents). Cumulative mortality rate at 30 days, 60 days, 3 months, and 1 year were compared between the groups.

Results: In the 1,644 patients, the cumulative mortality rate at 30 days, 60 days, 3 months, and 1 year was 0.1%, 0.5%, 0.7%, and 8.2%, respectively, in group I and 1.0%, 1.6%, 2.5%, and 8.8%, respectively, in group II (p = 0.02, p = 0.03. p = 0.01, and p = 0.72, respectively). In the 811 group II patients, the cumulative mortality rate at 30 days, 60 days, 3 months, and 1 year was 0.3%, 0.6%, 1.2%, and 6.6%, respectively, in group IIa; 0.8%, 1.6%, 2.1%, and 9.4%, respectively, in group IIb; and 4.1%, 5.1%, 8.2%, and 13.3%, respectively, in group IIc (p = 0.003, p = 0.01, p = 0.004, and p = 0.10, respectively).

Conclusions: CVD increases short-term mortality within 30 days, 60 days, and 3 months in elderly hip fracture patients. The use of anticoagulants in CVD patients increases the rate of surgical delay and short-term mortality within 30 days, 60 days, and 3 months.

Keywords: *Hip fracture, Anticoagulant, Cardiovascular disease, Mortality*

Hip fractures in elderly patient are associated with high mortality.[1] Some studies reported a 30-day mortality of 6% to 11%, and a 90-day mortality of up to 20%.[2,3] Surgical delay is known to increase mortality in elderly patients after hip fractures, and underlying disease is known to be chiefly responsible for surgical delay.[4]

Cardiovascular disease (CVD) and other comorbidities requiring anticoagulant medication are common in elderly patients.[1] Drugs such as aspirin and warfarin can prevent progression of CVD in elderly patients and are important to prevent venous thromboembolism after major orthopedic operation.[5,6] However, there are several problems related to these drugs, including increased mortality due to delayed surgery, perioperative bleeding problem (increased risk of surgical bleeding and spinal hematoma

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after spinal or epidural anesthesia), and mortality due to the underlying CVD itself.[1,7,8]

Various guidelines for elderly patients with hip fractures regarding whether to discontinue these drugs before surgery and the safe duration of discontinuation have been published.[1,9-11] However, there is still no consensus among the guidelines,[9] and the cause of increased mortality after hip fracture is not fully understood, even though some comorbidities, including CVD, have been suggested to be a possible cause of this phenomenon.[1,12,13] Moreover, studies on the effect of the type of anticoagulant on postoperative mortality show inconsistent results.[1,10,14] The purpose of this study is to compare postoperative mortality of hip fracture patients according to (1) the existence of CVD and (2) the type of anticoagulant used.

METHODS

The design and protocol of this retrospective study were approved by the Institutional Review Board of Seoul National University Bundang hospital (IRB No. B-1607/356-104). Informed consent was waived due to its retrospective nature. From January 2003 to December 2013, 2,357 patients (2,413 hips) who were treated for femoral intertrochanteric or neck fractures at two hospitals were enrolled in this retrospective observational study. The exclusion criteria included the following: (1) age under 60 years, (2) multiple fractures, (3) mortality before surgery, (4) conservative treatment or transfer to other hospital, (5) inappropriate medical records, (6) previous history of lower extremity surgery, and (7) pathologic fractures (Fig. 1). The included patients were grouped into group I (patients without CVD) and group II (patients with CVD). CVD included hypertensive disease (HTN), ischemic heart disease (IHD), other heart diseases, cerebrovascular disease, and other circulatory disease. Group II was sub-grouped into group IIa (patients without antiplatelet or anticoagulant), group IIb (patients on antiplatelets such as aspirin, clopidogrel, etc.), and group IIc (patients on anticoagulants such as warfarin and new oral anticoagulant [NOAC]). Demographic data, including age, sex, date of injury, operation date, type of surgery, type of fracture (femoral neck fracture or intertrochanteric fracture), modified Charlson comorbidity index,[15] duration of surgical delay, mortality rate (30 days, 60 days, 3 months, or 1 year), and past history of medication (aspirin, antiplatelet, or warfarin) were obtained by reviewing medical records and radiological findings. If the surgery was conducted within 2 days after injury, it was determined as not having surgical delay.

Medical comorbidity was assessed using a modified Charlson comorbidity index, which is calculated by summing points awarded for each disease condition as follows: one point for myocardial infarction, congestive heart failure, deep-vein thrombosis, peripheral vascular disease, dementia, chronic obstructive pulmonary disease, arthritis, ulcers, and diabetes; two points for cancer and stroke; and three points for liver cirrhosis.[15] Thus, possible total scores ranged from 0 to 15, where a higher score indicates worse health status. For internal fixation, cannulated screws (6.5-mm diameter), sliding hip screws, and intramedullary

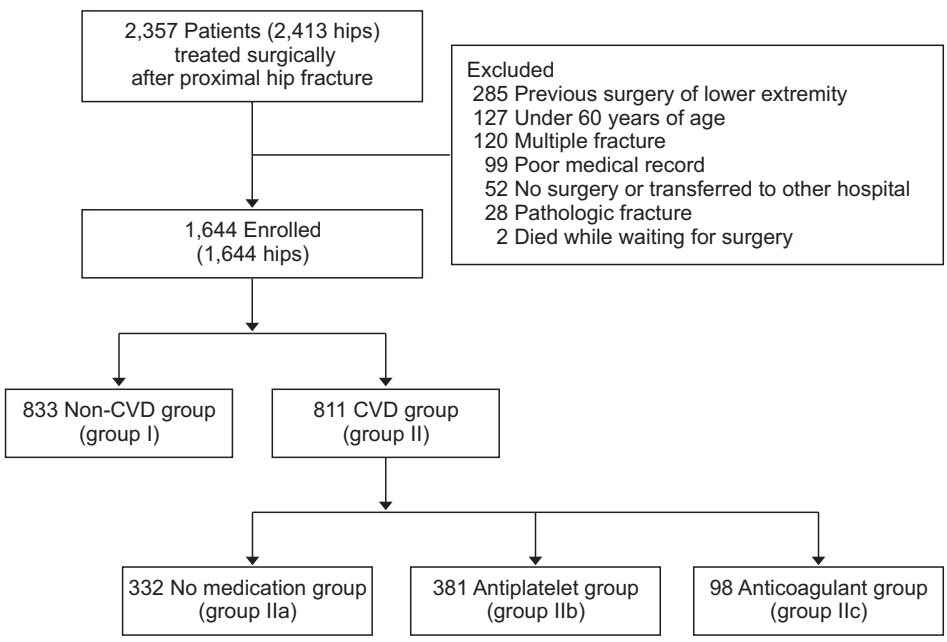

Fig. 1. Flowchart of study subjects. CVD: cardiovascular disease.

nails were used. For arthroplasty, bipolar hemiarthroplasty and total hip arthroplasty were used.

Anti-embolic pneumatic pumps were applied to all patients; they were encouraged to use the pumps in bed during hospitalization. No pharmacological prophylaxis for venous thromboembolism was conducted perioperatively. One day to 2 days after surgery, closed suction drainage was removed and the patients were mobilized with wheelchairs. Partial weight bearing ambulation with assistive devices (walker, crutches, or cane) was permitted 3 to 10 days after surgery. As their walking ability improved, their assistive devices were changed appropriately at the discretion of a physical therapist. Patients, who could not ambulate independently 1 week after the operation, were transferred to the rehabilitation unit for intensive ambulation training.

Routine outpatient clinic visit for follow-up was scheduled at 6 weeks and 3, 6, 9, and 12 months postoperatively, and every year thereafter. Patients unable to attend follow-up evaluations were interviewed by telephone. Clinical information was collected by one orthopedic surgeon (YHC) and two nurses (SYP, JHW). Mortality was checked using hospital records and/or by interviewing patient's family. A systemic search for death certificates at the National Statistical Office was conducted for patients lost to follow up.

Statistical Analysis

Chi-square test was used for the comparison of categorical variables and Student *t*-test and analysis of variance for continuous variables. A p-value < 0.05 was considered statistically significant. IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical calculations.

RESULTS

In total, 1,644 patients (1,644 hips) were included in this study. The study population comprised of 444 males (27%) and 1,200 females (73%). The mean age at injury was 78.7 ± 8.05 years (range, 60 to 107 years), and the fracture type was femoral neck fracture in 760 patients (46.2%) and intertrochanteric fracture in 884 patients (53.8%). The type of surgery was arthroplasty in 1,059 patients (64.4%) and reduction and internal fixation in 585 patients (35.6%).

The number of patients was 833 in group I (non-CVD) and 811 in group II (CVD group). Group II comprised of 482 patients (59.4%) with HTN, 129 patients (15.9%) with IHD, 267 patients with stroke (32.9%), and 55 patients with other diseases (6.8%). There was no statistical difference between the two groups in terms of the mean age, sex, operation method, and diagnosis (p > 0.05) (Table 1). However, group II showed higher Charlson comorbidity index and more surgical delay (p < 0.05). Also, the mortality rate was significantly higher in group II at 30

Table 1. Comparison of Mortality between Non-CVD Group (Group I) and CVD Group (Group II)

Variable	Group I (n = 833)	Group II (n = 811)	*p*-value
Age (yr)	78.33 ± 8.33	79.11 ± 7.74	0.22
Sex (male:female)	234:599	210:601	0.32
Diagnosis (neck:intertrochanter fracture)	382:451	376:435	0.84
Operation (internal fixation:arthroplasty)	195:638	390:421	0.32
Charlson comorbidity index	1.03 ± 0.75	1.77 ± 1.26	< 0.01
Surgical delay	502 (60.3)	531 (65.5)	0.03
Surgical delay time (day)	4.82 ± 16.87	5.16 ± 8.22	0.61
Mortality			
30 Days	1 (0.1)	8 (1.0)	0.02
60 Days	4 (0.5)	13 (1.6)	0.03
3 Months	6 (0.7)	20 (2.5)	0.01
1 Year	68 (8.2)	71 (8.8)	0.72

Values are presented as mean ± standard deviation or number (%).
CVD: cardiovascular disease.

Table 2. Comparison of Mortality According to the Type of Anticoagulant

Variable	Group IIa (n = 332)	*p*-value	Group IIb (n = 381)	*p*-value	Group IIc (n = 98)
Age (yr)	79.38 ± 7.68	0.66	78.86 ± 7.73	0.98	79.19 ± 8.03
Sex (male:female)	94:238	0.32	87:289	0.25	29:74
Diagnosis (neck:intertrochanter fracture)	158:174	0.79	169:12	0.51	49:49
Operation (internal fixation:arthroplasty)	157:175	0.49	190:191	0.72	48:50
Charlson comorbidity index	1.65 ± 1.12	0.14	1.84 ± 1.39	0.03	1.99 ± 1.29
Surgical delay	208 (62.7)	0.24	248 (65.1)	0.04	75 (76.5)
Surgical delay time (day)	4.44 ± 9.80	0.17	5.51 ± 7.14	0.09	6.21 ± 5.84
Mortality					
30 Days	1 (0.3)	0.80	3 (0.8)	0.003	4 (4.1)
60 Days	2 (0.6)	0.59	6 (1.6)	0.01	5 (5.1)
3 Months	4 (1.2)	0.74	8 (2.1)	0.04	8 (8.2)
1 Year	22 (6.6)	0.41	36 (9.4)	0.10	13 (13.3)

Values are presented as mean ± standard deviation or number (%).
Group IIa: no medication group, Group IIb: antiplatelet group, Group IIc: anticoagulant group.

days, 60 days, and 3 months ($p < 0.05$).

The number of patients in each subgroup of group II was 332 for group IIa, 381 for group IIb, and 98 for group IIc (Table 2). There was no statistical difference in terms of age, sex, operation method, and diagnosis among the three groups ($p > 0.05$). The Charlson comorbidity index and proportion of patients with surgical delay were significantly higher in group IIc ($p < 0.05$) and mortality at 30 days, 60 days, and 3 months were also highest in group IIc ($p < 0.05$).

DISCUSSION

The main findings of this study are as follows: (1) the CVD group had a higher Charlson comorbidity index, more surgical delay, and higher mortality rates at 30 days, 60 days, and 3 months after surgery compared to the non-CVD group; and (2) among the CVD subgroups, the anticoagulant group showed higher mortality rates at 30 days, 60 days, and 3 months after surgery than the other groups.

According to a European study, the incidence of hip fractures during 20 years of follow-up in patients over 50 years after diagnosis of CVD is 13 per 1,000 person-year.[12] One study from China reported that if older patients had an additional diagnosis of CVD, the risk of a hip fracture increased by 53%.[12] CVD events not only increase the risk of an accidental fall but also decrease walking ability, muscle strength, and perceptual function, leading to an increased risk of hip fractures.[16] In addition, many studies report CVD increases mortality after hip fractures.[17-20] Anticoagulant drug discontinuation for safe anesthesia and operation can lead to a sudden CVD event, resulting in increased mortality after hip fractures.[4,21] One study using the American College of Surgeons National Surgical Quality Improvement database reported that cardiac disease and stroke may increase the risk of postoperative cardiac events in hip fracture patients.[21] Another study reported that history of stroke, coronary artery disease, high blood pressure, and bleeding disorders were associated with inpatient stroke, and inpatient stroke was associated with increased mortality.[22] The results of this study also showed that the hip fracture patients with CVD had a higher Charlson comorbidity index, more surgical delay, and higher postoperative mortality in 30 days, 60 days, and 3 months.

Prophylactic medication for CVD is common in older people.[10] Drugs used in CVD include aspirin, clopidogrel, warfarin, and NOAC, and there are many debates about the effects of these drugs.[23-25] One study reported that there was significantly higher need for postoperative blood transfusion and higher first-year mortality in patients using aspirin before major hip surgery.[10] In hip fracture patients with warfarin medication, up to 11% of surgery was delayed beyond 48 hours because of high

international normalized ratio (international normalized ratio [INR] > 1.6).[6] An INR of > 1.6 increases the risk of perioperative bleeding and limits anesthetic options, as spinal or epidural anesthesia is contraindicated.[6] In one retrospective study, clopidogrel medication in older patients with hip fractures showed significant association with cardiac morbidity, with a peak risk of cardiac event at 4 and 8 days after the withdrawal of clopidogrel.[7] There was also a significant association between the length of preoperative withdrawal of clopidogrel and requirement for perioperative blood transfusion, with peak risk at postoperative day 1. Moreover, another study reported that 1-month and 1-year mortality rates were significantly higher in hip fracture patients having surgical delay beyond 72 hours.[10] Also, early surgery within 48 hours of admission was reported to reduce length of hospital stay, complication rates, and mortality.[26] In this study, group IIc (anticoagulant group) showed more surgical delay and higher postoperative mortality at 30 days, 60 days, and 3 months compared with the non-anticoagulant CVD patients. Although several methods including injection of vitamin K, fresh frozen plasma, or platelet concentration are available to reduce the effect of warfarin or NOAC for the purpose of reducing postoperative complications, the most important cause of mortality in elderly hip fracture patients with CVD is probably the severity of CVD itself.[10,27] Therefore, appropriate evaluation and management of these patients is mandatory during the perioperative period.

Our study has several limitations. First, this study is a retrospective study; therefore, there is a possibility of selection bias. However, we tried to minimize selection bias by enrolling patients using electronic medical record database and calculating mortality using systemic search for death certificates at the National Statistical Office. Second, medical comorbidities that may be related to the mortality rate in elderly populations were not analyzed individually in this study. However, we used the Charlson comorbidity index to minimize bias due to variously different medical conditions. Third, this study does not reflect discontinuation or duration of medication. Forth, the use of antiplatelet and anticoagulant drug was not allocated by randomization; these drugs were prescribed according to the condition of CVD. CVD increases short-term mortality within 30 days, 60 days, and 3 months in elderly hip fracture patients. The use of anticoagulants in CVD patients increases the rate of surgical delay and short-term mortality within 30 days, 60 days, and 3 months.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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