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Little Impact of Antiplatelet Agents on Venous Thromboembolism after Hip Fracture Surgery

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Since the late 1980s, low dose aspirin has been used to prevent stroke and ischemic heart disease. However, prophylactic effect of antiplatelets against venous thromboembolism (VTE), in patients who undergo hip fracture surgery (HFS) is controversial. Our purpose was to determine the incidence of symptomatic VTE after HFS and to evaluate whether antiplatelets reduce the development of symptomatic VTE following HFS. We retrospectively reviewed 858 HFS in 824 consecutive patients which were performed from May 2003 to April 2010 at an East Asian institute. We compared the incidence of symptomatic VTE in antiplatelet users and non-users using multivariate logistic regression analyses. Overall incidences of symptomatic pulmonary embolism including fatal pulmonary embolism, and symptomatic deep vein thrombosis in this study were 2.4% (21/858), and 3.5% (30/858), respectively. The incidence of symptomatic VTE was 4.8% (12/250) in antiplatelet users and 4.3% (26/608) in non-users (P = 0.718). It is suggested that antiplatelet agents are not effective in prevention of symptomatic VTE after HFS.

Key Words: Venous Thromboembolism; Venous Thrombosis; Pulmonary Embolism; Incidence; Hip Fractures; Antiplatelet Agents

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality after hip fracture surgery (HFS). Without any thromboprophylaxis, the risk of developing DVT following HFS is over 50% and that of developing PE is 7%-11% (1-3). Due to such a high incidence of VTE various thromboprophylactic modalities have been recommended by several guidelines, including the American Academy of Orthopaedic Surgeons (AAOS), the American College of Chest Physicians (ACCP), and National Institute for Health and Clinical Excellence (NICE) (3-5).

In contrast to the large number of studies on developing symptomatic VTE following HFS from Western countries, very few studies have been reported from East Asia.

Daily use of low dose aspirin to prevent thrombosis became popular even in healthy people without any history of cardiovascular disease or cerebrovascular accident since the late 1980s (6, 7). However, thromboprophylactic efficacy of antiplatelets in patients who undergo HFS is controversial (3-5).

The purpose of this study was to determine the incidence of symptomatic VTE after HFS and to evaluate whether antiplatelet users have a low incidence of symptomatic VTE (symptomatic DVT, PE and fatal PE) after HFS than non-users in Korean population.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 851 patients (887 hips), who underwent HFS for femoral neck and intertrochanteric fractures at single institute from May 2003 to April 2010. Twenty-eight patients (29 hips) who were treated with anticoagulant, such as heparin and warfarin; 11 patients (11 hips) due to management for cerebro-vascular disease, 10 patients (11 hips) due to a history of thrombo-embolic event, 6 patients (6 hips) due to a cardiac disease and one patients (one hip) due to femoro-popliteal bypass graft before surgery were excluded, leaving 824 patients for the study.

Of the 824 patients (858 hips), antiplatelet users were defined as those who had taken low-dose aspirin (81-100 mg) or other antiplatelet agents for the prevention of thrombotic cardiovascular or cerebrovascular event before admission for HFS, stopped the antiplatelet medication 5 to 7 days prior to surgery, and resumed medication 1 day to 3 days after the surgery. Two hundred and forty five patients (250 hips) were identified as antiplatelet users. The remaining 579 patients (608 hips) were classified

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as non-users.

In the antiplatelet users, there were 173 women and 72 men with a mean age of 77.6 yr at the time of operation. Their mean body mass index (BMI) was 22.1 kg/m^2. In the non-users, there were 414 women and 165 men with a mean age of 75.2 yr at the time of operation. Their mean BMI was 21.3 kg/m^2 (Table 1).

No pharmacological or mechanical prophylaxis for VTE other than antiplatelet was done postoperatively in both groups. However, thigh-length antiembolic stockings were applied and the ankle pump was encouraged in bed during the hospitalization.

One day to three days after the operation, closed suction drainage was removed and patients were mobilized with wheelchairs. Patients walked with restricted weight-bearing and use of assistive devices (wheelchair, walker, crutches, or cane) 3 to 10 days after the operation. As their walking ability improved, their assistive devices were changed appropriately by physical therapists.

After the operation, we carefully monitored clinical signs of DVT including pain and tenderness in the calf or thigh, swelling or erythema of the operated limb, and a positive Homans' sign. When VTE was suspected, we consulted the patients to cardiovascular physicians. A diagnosis of DVT was made using duplex ultrasonography or lower extremity CT angiography. A PE was confirmed by a ventilation/perfusion scan or pulmonary CT angiography. Patients who were diagnosed as having a DVT or PE were treated with warfarin.

Most deaths due to PE related to the operation reportedly occur within 3 months and any death of unknown cause that occurred within 3 months of operation is considered to be the result of PE (8-10). We confirmed the fatal PE, if present, from the death certificate.

Patients were monitored for 1 week to 3 weeks in the ward. After discharge, patients were routinely followed at 6 weeks, 3 months and 6 months after the operation with a specific interest of VTE. Patients who had not returned on regularly scheduled visits were contacted by telephone.

We compared the incidence of symptomatic VTE (DVT, PE and fatal PE) in both groups. We also assessed gender, age, BMI, ambulatory ability before injury according to Koval's categories (11), type of fracture (femur neck fracture or intertrochanteric fracture), pathologic fracture, malignancy, type of surgery (arthroplasty or internal fixation), type of anesthesia (regional or general), co-morbidity assessed by American Society of Anesthesiologists (ASA) score, operation time, the length of time from fracture to surgery, and previous history of cerebrovascular or cardiovascular disease to determine the relationships between these variables and the development of VTE.

Table 1. Characteristics of antiplatelet users and non-users

Parameters	Antiplatelet users	Non-users
Gender		
Male	72	165
Female	173	414
Age (yr)	77.6 (50-94)	75.2 (17-107)
BMI (kg/m^2)	22.1 (14.4-31.4)	21.3 (12.1-29.8)

BMI, body mass index.

Statistical analyses were planned to determine whether the perioperative use of antiplatelets reduced the incidence of symptomatic VTE. All HFS were divided into 2 groups; the VTE group (symptomatic DVT, PE as well as fatal PE) and non-VTE group. To determine confounding factors, univariate comparisons between the VTE group and the non-VTE group were made based on the demographic data and operative parameters. Statistical significance of the differences between the 2 groups was determined by chi-square test for categorical variables and Student's t-test for continuous variables. For the variables with a *P* value less than 0.1 in the univariate analyses, multivariate logistic regression analyses using the enter method were performed. In the multivariate logistic regression, the dependent variable was whether the VTE occurred or not postoperatively. From the multivariate regression analyses, it was assessed whether use of antiplatelet statistically reduced occurrence of VTE. Statistical analyses were conducted with the SPSS for Windows statistical package (version 12.0; SPSS, Chicago, IL, USA), and *P* value less than 0.05 was considered as significant.

Ethics statement

The design and protocol of this study were reviewed and approved by the institutional review board of the Seoul National University Bundang Hospital (IRB No. B-1006-103-118). The board waived informed consent.

RESULTS

Among the 858 procedures, there were 4 deaths of unknown cause within 3 months after the HFS. Symptomatic DVT occurred in 30 patients. Of them, 13 patients suffered symptomatic PE. Four patients suffered symptomatic PE without DVT. Overall incidences of symptomatic PE including fatal PE, and symptomatic DVT in this study were 2.4% (21/858), and 3.5% (30/858), respectively. The incidence of symptomatic VTE was 4.8% (12/250) in antiplatelet users and 4.3% (26/608) in non-users (*P* = 0.718). In the univariate comparisons, only gender showed *P* value less than 0.1 (Table 2).

Multivariate logistic regression analyses for the variables with a *P* value less than 0.1 in the univariate analyses demonstrated that no variable was significantly associated with the VTE. Besides use of antiplatelet, the independent variables tested for the multivariate logistic regression analyses included age, gender, and BMI, as confounding factors (Table 3). The value of R2 coefficient for this multivariate regression model was 0.009, suggesting that this multivariate model would explain the variation of the outcome variable to the extent of 0.9%.

After multivariate logistic regression analyses, use of antiplate-

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let was not associated with symptomatic VTE in HFS patients (P = 0.841).

DISCUSSION

In this study, the overall incidence of symptomatic VTE following HFS was 4.4% (38/858), and the perioperative use of antiplatelet did not reduce the incidence of symptomatic VTE after HFS in Korean patients.

Pulmonary Embolism Prevention (PEP) study, which compared the efficacy of low-dose aspirin and placebo in patients undergoing HFS, presented that the aspirin reduced the risk of VTE (12). However, the symptomatic VTE after HFS was not reduced in Korean patients who received antiplatelet agent including aspirin in this study.

On the other hand, the 4.4% overall incidence of VTE in this study is lower than that (46%-60%) after HFS without thromboprophylaxis in Western patients, and comparable with that (1.3%-6%) after HFS in Western patients, who underwent routine thromboprophylaxis (1, 12-16). Although several risk factors for VTE have been presented by previous studies, there was no significant risk factor of VTE in HFS after multivariate analysis in this study.

In terms of HFS, recent Asian studies suggested that the incidence of VTE in Asian patients was similar to that reported from the West (17-21) (Table 4). However, the majority of these studies mainly focused on other procedure such as total knee arthroplasty and total hip arthroplasty, and had too small size of HFS. In addition, most studies used data collected from various areas of Asia and included multiple ethnic groups other than East Asian. In the AIDA study, which evaluated asymptomatic VTE in 837 Asian patients undergoing orthopedic surgery in 19 centers in 7 Asian countries, the rate of asymptomatic DVT in 96 HFS without thromboprophylaxis was 42.0%, which was similar to that from West (Table 4) (20).

Although the incidence (4.4%) of symptomatic VTE in this study was lower than those of the Western studies, our results do not indicate that thromboprophylaxis after HFS is not necessary in Korean patients, because the incidence of symptomatic VTE will always be markedly lower than those of asymptomatic VTE, that are venographically proved. In contrast to elective total hip arthroplasty, the patients with HFS were extremely old and had several co-morbidities such as diabetes and cardiovas-

Table 2. Univariate comparisons between VTE group and non-VTE group

Variables	VTE group (n = 38)	Non-VTE group (n = 820)	P value
Gender			0.097
Male	6	236	
Female	32	584	
Age (yr)	79.1 ± 9.8	75.9 ± 12.2	0.115
BMI (kg/m^2)	22.2 ± 4.1	21.5 ± 3.7	0.235
Koval classification	2.4 ± 1.7	2.5 ± 1.9	0.894
Diagnosis			0.619
Femoral neck fracture	15	362	
Intertrochanteric fracture	23	458	
Pathologic fracture			1.000
No	38	801	
Yes	0	18	
Malignancy			0.364
No	33	752	
Yes	5	68	
Type of operation			0.208
Arthroplasty	34	655	
Internal fixation	4	165	
Anesthesia			0.150
Regional (spinal/epidural)	36	701	
General	2	119	
ASA	2.3 ± 0.6	2.2 ± 0.7	0.683
Operation time (min)	87.6 ± 23.2	95.7 ± 36.8	0.202
Duration from fracture to operation (days)	8.4 ± 12.8	10.3 ± 36.7	0.753
Previous cardiovascular or cerebrovascular disease			0.832
No	32	662	
Yes	6	158	
Antiplatelet			0.718
User	12	238	
Non-user	26	582	

VTE, venous thromboembolism; BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 3. Multivatriate analysis for symptomatic VTE

Variables	Odds ratio (95% CI)	P value
Male	0.548 (0.223-1.346)	0.189
Age	1.031 (0.994-1.346)	0.101
BMI	1.066 (0.976-1.164)	0.157
Use of antiplatelet	0.930 (0.457-1.893)	0.841

VTE, venous thromboembolism; CI, confidence interval; BMI, body mass index.

Table 4. Incidence of symptomatic VTE after hip fracture surgery in previous studies and the current study

Authors (reference No.)	No. of HFS	No. of VTE (%)	No. of DVT (%)	No. of PE (%)
Atichartakarn et al. (1988) (17)	29	2 (6.9)*	0 (0)	NA
Mitra et al. (1988) (18)	72	7 (9.7)*	7 (9.7)*	0
Dhillon et al. (1996) (19)	40	20 (50)*	20 (50)*	0
Piovella et al. (2005) (20)	96	40 (42)*	40 (42)*	NA
Bagaria et al. (2006) (21)	102	7 (6.8)*	7 (6.8)*	0
Current study	858	38 (4.4)	30 (3.5)	21 (2.4)

*Including asymptomatic DVT. VTE, venous thromboembolism; HFS, hip fracture surgery; THA, total hip arthroplasty; DVT, deep vein thrombosis; PE, pulmonary embolism; NA, not available.

cular diseases. If these patients suffered symptomatic VTE, their recovery of ambulatory ability prior to injury would be delayed during rehabilitation, and the mortality of the patients with osteoporotic hip fracture would be increased (9, 22).

This study has several limitations. First, our study was not a prospective but a retrospective study. However, a prospective randomized comparative study is barely possible in these senile patients who have a lack of perception on participation. Second, we could not perform VTE studies in asymptomatic patients and did not determine the incidence of asymptomatic VTE. However, VTE studies are associated with procedure-related complications and high medical cost (23, 24), and objectives of prophylaxis in VTE are to prevent fatal PE and to reduce the symptomatic morbidity associated with VTE (25). Therefore, our study on symptomatic VTE in patients with HFS might be justified. Third, subgroup analyses according to antiplatelet agents and their doses were not performed because our patients were treated with various agents and the number of symptomatic patients was small. Fourth, we did not evaluate the patients' compliance in terms of the antiembolic stockings and the ankle pump, which might be a confounding factor for VTE development.

Although antiplatelet therapy has been shown to reduce the risk of arterial occlusive disease (6, 7, 26), it is controversial whether the antiplatelet agents are effective or not in the prevention of VTE (12, 27, 28). It might be argued that the antiplatelet users in our study might have a previous history of major arterial occlusive diseases including cerebrovascular or cardiovascular disease and were more vulnerable to VTE. However, univariate analysis in our study showed that previous arterial disease was not associated with an increased risk of VTE.

The incidence of hip fracture will increase in accordance with prolonged life expectancy in East Asia (29, 30), and VTE after HFS appears as an important medical issue. Our study showed that antiplatelets are not effective in the prevention of symptomatic VTE after HFS, although the incidence of symptomatic VTE after HFS was low. The data of current study could be used for the thromboprophylactic guideline of in Korean patients with HFS.

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AUTHOR SUMMARY

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