Thromboprophylaxis After Hip Fracture: Evaluation of 3 Pharmacologic Agents

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Abstract

We compared the clinical efficacy and side-effect profiles of aspirin, dextran 40, and low-molecular-weight heparin (enoxaparin) in preventing thromboembolic phenomena after hip fracture surgery.

All patients admitted with a diagnosis of hip fracture to our institution between July 1, 1987, and December 31, 1999, were evaluated. Study inclusion criteria were age 65 years or older, previously ambulatory, cognitively intact, home-dwelling, and having a nonpathologic intertrochanteric or femoral neck fracture. Each patient received mechanical thromboprophylaxis (above-knee elastic stockings) and 1 pharmacologic agent (aspirin, dextran 40, or enoxaparin); patients who received aspirin were also given a calf sequential compression device. Meeting the selection criteria and included in the study were 917 patients.

Findings included low incidence of thromboembolic phenomena (deep vein thrombosis, 0.5%-1.7%; pulmonary embolism, 0%-2.0%; fatal pulmonary embolism, 0%-0.5%) and no difference among the 3 pharmacologic agents in thromboembolic prophylaxis efficacy. Use of enoxaparin was associated with a significant increase (3.8%) in wound hematoma compared with dextran 40 (1.6%) and aspirin (2.4%) (P<.01). The 3 agents were found not to differ with respect to mortality, thromboembolic phenomena, hemorrhagic complications, or wound complications.

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Patients sustaining hip fractures are at substantial risk for developing deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT incidence up to 62% and PE incidence up to 24% have been reported in these patients.[1-3] The numerous pharmacologic and mechanical modalities that have been reported to decrease postoperative DVT incidence include warfarin, aspirin, dextran 40, low-molecular-weight heparin (LMWH), and mechanical compression devices.[4-9] Although multiple studies have compared various pharmacologic and mechanical agents for thromboprophylaxis after hip and knee replacement, fewer studies have directly compared these agents after hip fracture surgery.[9-13] Many of these hip fracture studies have compared either one agent against placebo or one agent at different doses or treatment durations.[6-8,14-17] The number of studies comparing different pharmacologic agents is limited, and the results of these studies have not yet clarified which thromboprophylactic agent is preferable.[1,5,18-20]

Although it is well accepted that a pharmacologic agent can decrease the incidence of postoperative venous thromboembolism (VTE), the optimal agent to use after hip fracture surgery is controversial.

In the study reported here, we compared the clinical efficacy and side-effect profiles of aspirin, dextran 40, and enoxaparin (an LMWH) in preventing thromboembolic phenomena after hip fracture surgery.

Materials and Methods

All patients admitted to our institution with a diagnosis of hip fracture were evaluated for inclusion in the study. Inclusion criteria were age 65 or older, femoral neck or intertrochanteric hip fracture of nonpathologic origin, ambulatory before fracture, cognitively intact, and living in own home or apartment before fracture. Procedures used for the study were reviewed and approved by the Institutional Review Board of the hospital before initiation of the investigation. All patients were identified at the time of admission and prospectively followed. Preinjury data were collected at time of admission by patient and/or family interview. Hospitalization data were collected during hospitalization and at discharge.

From July 1987 to December 1993, the anticoagulants aspirin and dextran 40 were used. The oral aspirin tablet dosage was 325 mg once per day. The intravenous dextran 40 dosage was 50 g in 500 mL of saline once per day. Enoxaparin became the primary thromboprophylactic agent in January 1994. The subcutaneous enoxaparin

dosage was 30 mg twice per day. Selection of aspirin, dextran 40, or enoxaparin was based on surgeon preference. Above-knee elastic stockings were placed on all patients perioperatively, and a calf sequential compression device (SCD) was used for each patient who was taking aspirin for thromboprophylaxis. All patients followed a protocol of early mobilization on postoperative day 1, with weight-bearing ambulation as tolerated.

Examined patient characteristics included age (65-84 or 85+ years), sex, prefracture ambulatory status, status of prefracture basic and instrumental activities of daily living (BADLs and IADLs, respectively), and American Society of Anesthesiologists (ASA) rating of operative risk (1-2 or 3-4). BADLs included feeding, dressing, toileting, and bathing,[21] and IADLs included food shopping, food preparation, use of public transportation, banking and finances, and housework.[22] Each BADL and IADL was rated on a 5-point scale ranging from 0 (complete dependence in that activity) to 4 (complete independence). Categories were dichotomized such that a score of 3 or 4 points indicated that the patient was independent in an activity, while a score of 0, 1, or 2 points indicated the patient's dependence in that activity. The number of BADLs and IADLs in which the patient was dependent was recorded.

General health status was defined by number of preexisting significant comorbid conditions, which included diabetes mellitus, congestive heart failure, cardiac arrhythmias, ischemic heart disease, previous cerebrovascular accident, renal disease, cancer, Parkinson disease, hypertension, and chronic obstructive pulmonary disease. These comorbidities were chosen as the most important based on our experience and the literature.[7,23] Previous studies have shown that patients with 0, 1, or 2 comorbidities had similar mortality outcomes, so comorbidities were collapsed into 2 categories (0-2 or 3+).[24] Recorded operative data included fracture type (intertrochanteric or femoral neck), procedure (fracture fixation or prosthetic replacement), anesthesia (spinal or general), blood loss, units of blood transfused, and operative time.

Outcomes in 2 categories were examined—thromboprophylaxis efficacy (including incidence of symptomatic DVT, PE, and fatal PE) and other postoperative complications (including incidence of wound infection, wound hematoma, persistent wound drainage, gastrointestinal (GI) bleeding, thrombocytopenia, intracranial bleed, and mortality). Each day, each patient underwent evaluation for calf/thigh tenderness, increasing lower extremity edema, and pain with forced dorsiflexion of the ankle. This evaluation was performed in conjunction with patient history (including prior DVT, active neoplasm, and prolonged perioperative immobilization). For patients who developed dyspnea, chest pain, or mental status changes after surgery, workups were done in conjunction with the medical service at the hospital. Suspicion for PE rose in the setting of vital sign abnormalities (tachycardia, hypotension, low O_2 saturation), electrocardiogram abnormalities, widened A-a gradient on room air arterial blood gas, or poor response to supplemental oxygen. Clinical suspicion for DVT and PE was followed by radiographic confirmation through, respectively, ultrasonography and angiography.

Data were analyzed using the thromboprophylactic agent as predictor and each of the aforementioned measures as outcome by means of χ^2 analysis and/or Student *t* test when appropriate. Multiple logistic regression was performed to estimate the simultaneous effects of important covariates. Only variables that added significantly to the prediction were retained in the final model. *P*s≤.05 were considered significant. All statistical analyses were performed using SAS software (Version 8, SAS Institute, Inc, Cary, NC).

Results

From July 1, 1987, through December 31, 1999, 954 patients with a diagnosis of hip fracture were admitted to our institution. Of these patients, 917 met the criteria for study inclusion. Of the 917 study participants, 238 (26.0%) were placed on enoxaparin, 125 (13.6%) on aspirin, and 554 (60.4%) on dextran 40. Preinjury characteristics are summarized in Table I. Mean age was 79.7 years. Patients on aspirin were more likely to be age 85 or older (*P*<.01) and dependent on IADLs (*P*<.01), and patients on enoxaparin were more likely to have a higher ASA classification (3 or 4) (*P* = .048). The 3 groups did not differ with respect to sex, number of comorbidities, BADL dependence, and prefracture ambulatory status.

Operative data are summarized in Table II. The 3 groups did not differ with respect to fracture type, procedure type, intraoperative blood loss, operative time, and units of blood transfused. Patients on enoxaparin were more likely to have received spinal anesthesia (*P*<.01).

Outcome results were divided into incidence of thromboembolic events, which evaluated the efficacy of each agent in VTE prophylaxis, and incidence of complications, which included wound complications, bleeding complications, and mortality. Twenty-five (2.7%) of the 917 patients died in the hospital. Fourteen patients (1.5%) required revision surgery, 9 (1.0%) developed a DVT, 14 (1.4%) had a PE, and 4 (0.4%) had a fatal PE. Sixteen patients (1.7%) developed a wound infection. Patients on enoxaparin were more likely to form a postoperative wound hematoma (*P*<.01). There were no differences in hospital mortality or in any of the aforementioned complications among the enoxaparin, aspirin, and dextran 40 groups. No one sustained a GI bleed or PE in the aspirin group, though this finding was not statistically significant when compared with dextran 40 and enoxaparin (Table III).

Discussion

VTE prevention using mechanical and pharmacologic agents in elective total joint arthroplasty has been studied extensively.[7,9-13] In comparison, studies of thromboprophylaxis after hip fracture surgery have been limited. Investigators have reported the efficacy of various pharmacologic agents (eg, vitamin K antagonists, polysaccharide plasma expanders, LMWH, aspirin) in preventing VTE in

Table I. General Characteristics of the Population*

Characteristic	Total Population	Agent Group			P
		Aspirin	Dextran 40	Enoxaparin	
N	917	125 (13.6%)	554 (60.4%)	238 (26.0%)	
Age, y (mean±SD)	79.7±7.4	81.7±7.7	79.2±7.1	79.9±7.7	
Age					
65-84 y	667 (72.7%)	77 (61.6%)	428 (77.3%)	162 (68.1%)	<.01
85+ y	250 (27.3%)	48 (38.4%)	126 (22.7%)	76 (31.9%)	
Sex					
Female	727 (79.3%)	106 (84.8%)	432 (78.0%)	189 (79.4%)	NS
Male	190 (20.7%)	19 (15.2%)	122 (22.0%)	49 (20.6%)	
ASA operative risk					
1, 2	475 (53.7%)	63 (50.8%)	304 (56.9%)	108 (47.6%)	.048
3, 4	410 (46.3%)	61 (49.2%)	230 (43.1%)	119 (52.4%)	
Comorbidities					
0, 1, 2	748 (81.6%)	99 (79.2%)	463 (83.6%)	186 (78.2%)	NS
3+	169 (18.4%)	26 (20.8%)	91 (16.4%)	52 (21.8%)	
Prefracture ambulation					
Community	812 (88.6%)	111 (88.8%)	495 (89.4%)	206 (86.6%)	NS
Home	105 (11.4%)	14 (11.2%)	59 (10.6%)	32 (13.4%)	
Prefracture BADLs					
Independent	737 (83.7%)	95 (76.6%)	459 (84.2%)	183 (86.3%)	NS
Dependent	144 (16.4%)	29 (23.4%)	86 (15.8%)	29 (13.7%)	
Prefracture IADLs					
Independent	522 (52.3%)	54 (43.6%)	321 (58.9%)	147 (69.3%)	<.01
Dependent	359 (40.8%)	70 (56.4%)	224 (41.1%)	65 (30.7%)	

*ASA indicates American Society of Anesthesiologists; BADL, basic activity of daily living; IADL, instrumental activity of daily living; NS, not significant.

patients with hip fracture.[1,4,8,14-16,20] Many studies of hip fracture have compared either one agent against placebo or different doses of the same agent.[4,8,14,15,17]

The number of studies comparing different pharmacologic agents is limited, and the results of these studies have not yet clarified which thromboprophylactic agent is preferable.[1,5,18-20] Bergqvist and colleagues[25] found that, compared with dextran 70, an LMWH (Org 10172) had a significantly better thromboprophylactic effect and side-effect profile with respect to postoperative blood transfusions. DVT incidence was 10% in the LMWH group versus 30% in the dextran 70 group. The postoperative transfusion requirement was higher in the dextran 70 group, but there were no other differences in bleeding complications between the 2 groups. Gerhart and colleagues[18] found lower DVT incidence with the same LMWH (Org 10172)

Table II. Operative Data*

Data	Total Population	Agent Group			P
		Aspirin	Dextran 40	Enoxaparin	
Fracture type					
Femoral neck	460 (50.2%)	66 (52.8%)	284 (51.3%)	110 (46.2%)	NS
Intertrochanteric	457 (49.8%)	59 (47.2%)	270 (48.7%)	128 (53.8%)	
Procedure					
Prosthetic replacement	297 (32.4%)	37 (29.6%)	191 (34.5%)	69 (29.0%)	NS
Plate/screws	620 (67.6%)	88 (70.4%)	363 (65.5%)	169 (71.0%)	
Anesthesia					
General	423 (47.0%)	62 (51.2%)	288 (52.4%)	73 (31.9%)	<.01
Spinal	477 (53.0%)	59 (48.8%)	262 (47.6%)	156 (68.1%)	
Estimated blood loss (mean), mL	303	298.5	338.4	220	NS
Operative time (mean), min	102.3	98.9	106.2	94.7	NS
Units transfused (mean)	0.8	0.6	0.8	0.9	NS

*NS indicates not significant.

Table III. Incidence of Thromboembolic Events and Complications*

Outcome	Total Population	Agent Group			P
		Aspirin	Dextran 40	Enoxaparin	
Thromboembolic event					
Deep vein thrombosis	9 (1.0%)	(0%)	9 (1.6%)	5 (2.0%)	NS
Pulmonary embolism	14 (1.5%)	0 (0%)	9 (1.6%)	5 (2.0%)	NS
Fatal pulmonary embolism	4 (0.4%)	0 (0%)	3 (0.5%)	1 (0.4%)	NS
Complication					
Wound drainage >7 days	31 (6.7%)†	4 (3.2%)	21 (4.6%)	4 (1.7%)	NS
Wound infection	16 (1.8%)†	2 (1.6%)	8 (1.4%)	6 (2.5%)	NS
Wound hematoma	21 (3.7%)†	3 (2.4%)	9 (1.6%)	9 (3.8%)	<.01
Gastrointestinal bleeding	16 (2.7%)†	0 (0%)	14 (2.4%)	2 (0.4%)	NS
Thrombocytopenia	16 (2.7%)†	4 (3.2%)	8 (1.4%)	4 (1.7%)	NS
Cranial bleed	3 (0.5%)	0 (0%)	3 (0.5%)	0 (0%)	NS

*NS indicates not significant. †Percentages do not represent the total of 917 patients because of missing data.

versus warfarin (7% and 21%, respectively) but no significant differences in PE or major bleeding complications. Gent and colleagues[1] found lower DVT incidence with the same LMWH (27.8%) versus aspirin (44.3%) ($P = .028$) but no significant differences in proximal vein thrombosis, PE, or bleeding complications.

However, in a randomized, prospective, double-blind trial, Monreal and colleagues[19] found that LMWH was less effective than conventional low-dose heparin in DVT prevention and PE prevention (both differences were statistically significant). The 2 groups did not differ with respect to mortality or bleeding complications. Powers and colleagues[20] found aspirin (10.6%) as safe and effective as warfarin (9.2%) in preventing proximal vein thrombosis and PE in patients with hip fracture, though overall VTE incidence was higher with aspirin (40.9%) than warfarin (20.0%).

The results from these comparative studies are difficult to interpret because of the different medication dosages, dosing regimens, population data, rehabilitation protocols, and modalities in detecting thromboembolic phenomena. The optimal pharmacologic agent remains controversial. Our investigation comparing aspirin, dextran 40, and an LMWH (enoxaparin) had specific advantages in that (a) by defining specific and strict inclusion criteria, we were able to define a more homogenous group, perhaps more reflective of the majority of geriatric patients who sustain hip fractures than in previous studies, and (b) all patients followed a similar postoperative rehabilitation protocol consisting of early weight-bearing ambulation as tolerated.

In this study, we found that aspirin, dextran 40, and enoxaparin all had a low incidence of thromboembolic phenomena (DVT, PE, fatal PE). Incidence of wound hematoma was statistically significantly ($P = .003$) higher for enoxaparin (3.8%) than dextran 40 (1.6%) and aspirin (2.4%). Otherwise, the 3 pharmacologic agents did not differ significantly in complications or side effects, including hemorrhagic complications, platelet dysfunction, and mortality. No patients on aspirin sustained a PE, GI bleed, or intracranial hemorrhage. As the incidence of these complications was low, however, this study might have lacked the statistical power to detect a significant difference among the 3 agents.

Overall DVT incidence was approximately 1%, lower than the 7% to 44% reported in other studies using various pharmacologic agents.[1-3,20,25] Three factors might account for the difference:

1. In our study, DVT detection was based on clinically significant or symptomatic DVT considered in the context of patient history and then confirmed with ultrasonography and/or venography. We effectively stratified our patients according to clinical signs and risk factors for developing DVT—a methodology reported on by other authors.[7,8,26-28] Wells and colleagues[28] described a clinical prediction algorithm demonstrating 94% sensitivity of ultrasonography for detecting DVT in high-risk patients and 100% posttest probability of DVT with an abnormal ultrasound in the high-risk group; the sensitivity of this modality decreased in the lower risk strata. Previous studies have included both symptomatic and asymptomatic DVT, as most or all patients underwent a postoperative imaging study. These studies also included distal DVT, which in comparison with proximal DVT has been found to have little clinical significance in PE development.[1,4,6,14,18,20,25] In studies of the incidence of clinically apparent, symptomatic DVT, rates have been as low as 0.6%.[7,8]

2. Each evaluated pharmacologic agent was used in conjunction with mechanical thromboprophylaxis, and patients on aspirin also received a calf SCD. Efficacy of mechanical thromboprophylaxis alone and in conjunction with a pharmacologic agent has been described.[6,29,30]

3. We instituted an aggressive rehabilitation protocol of unrestricted weight-bearing ambulation beginning on postoperative day 1.[31] Inability to ambulate full weight was not an exclusionary criteria for this study. Early mobilization may be one reason that incidence of thromboembolic complications was decreased.

An important limitation of this study is that, though our data were collected prospectively, we did not randomly assign patients to the 3 prophylactic agents. Agent selection was based only on surgeon preference, and no protocol existed for randomizing patients to a particular agent based on their preoperative risk for developing DVT. However, inclusion criteria, surgeons, and postoperative rehabilita-

tion remained the same throughout the entire study period. Furthermore, multivariate analyses were performed to control for the differences in patient characteristics.

Another important limitation of this study is that there were too few enrolled patients to detect a significant difference in thromboembolic episodes. Power analysis results showed that thousands of patients would need to be enrolled to produce significant differences given the relatively low incidence of thromboembolic episodes in this study. However, we believe that the comparably low incidence of thromboembolic phenomena with the 3 pharmacologic agents demonstrates that all were effective in thromboprophylaxis for patients with hip fracture. Our findings on the thromboprophylactic efficacy of aspirin seem to corroborate results from a recent randomized prospective study of 13,356 patients with hip fracture—a study with a sample size large enough to detect a significant difference in clinical efficacy of aspirin over placebo.[7] In that study, compared with placebo, aspirin was associated with a 43% reduction in pulmonary emboli and a 29% reduction in symptomatic DVT during hospitalization, and there was no significant increase in wound hematoma, wound infection, or wound drainage more than 4 days after surgery.

As there was a low incidence of clinically evident thromboembolic phenomena with all 3 agents studied, and the side-effect profile of aspirin was significantly better than that of enoxaparin, aspirin is more attractive than an LMWH or dextran 40. Aspirin is safe, inexpensive (~$0.09 per tablet at our institution), and easy to administer; enoxaparin is more expensive (~$12.28 per dose or $24.56 per day at our institution) and requires twice-daily subcutaneous injections; and dextran 40 has not gained wide acceptance because of its high cost (~$16.12 per dose), need for intravenous administration, and potential side effects, including congestive heart failure and increased transfusion requirements.[9,25] (Although use of dextran 40 after hip surgery is limited at most centers, we included the agent in our study because of reports of its thromboprophylactic efficacy and its previously extensive use for DVT prophylaxis at our institution.[5])

Furthermore, it has been extensively reported that aspirin has benefits other than VTE prevention.[32-35] Many geriatric patients are on aspirin for cardiovascular or cerebrovascular disease. As aspirin is given to many geriatric patients, who are usually on multiple chronic medications, its use eliminates the need for additional medication and reduces the risks for adverse side effects and drug interactions. Our study results are also pertinent to geriatric patients with an allergy or sensitivity to any of the reviewed pharmacologic agents. A patient with an aspirin allergy or a thrombocytopenic side effect secondary to heparin can be given an alternative medication with no expected significant difference in efficacy of thromboembolic prophylaxis.

Conclusions

Few studies have directly compared different pharmacologic agents in preventing VTE after hip fracture surgery. In the study reported here, we found that aspirin, dextran 40, and enoxaparin all had a low incidence of clinically evident thromboembolic phenomena after hip fracture surgery but did not differ significantly in mortality, wound complications, or bleeding complications. Wound hematoma formation was the exception: Enoxaparin showed a significant increase compared with aspirin and dextran 40 ($P<.01$). Our study results may have additional clinical significance with respect to health care costs, geriatric patients on multiple medications, and geriatric patients with drug allergies or sensitivities.

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None of the authors has a financial or proprietary interest in the subject matter or materials discussed in the article—including but not limited to employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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This paper will be judged for the Resident Writer's Award.