Risk of clinical pulmonary embolism after joint surgery in patients receiving low-molecular-weight heparin prophylaxis in hospital

A 10-year prospective register of 3,954 patients

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ABSTRACT We studied the incidence of nonfatal, radiologically-confirmed, clinical pulmonary embolism (PE) after major joint surgery during 10 years of observation. The findings are based on a prospective register of all patients undergoing total hip replacement (THR), total knee replacement (TKR), or nailed hip fracture (NHF) in a Scandinavian hospital between 1989 and 1998. All patients received thromboprophylaxis with low-molecular-weight heparin, continued until discharge. Patients with suspected PE underwent ventilation/perfusion scintigraphy and/or spiral CT. Patients with concomitant clinical signs of deep vein thrombosis (DVT) were also subjected to imaging diagnostics. 3,954 patients underwent THR, TKR, or NHF; 122 of them were readmitted on clinical suspicion of PE, and 50 cases were confirmed. Of patients with confirmed PE, 6/50 had DVT. The average time to readmission was 35 (5–94) days after THR, 24 (1–173) days after NHF, and 9 (2–17) days after TKR. Following major hip surgery, the incidence of PE remained high for at least 2–3 months (less following TKR) in those given thromboprophylaxis for about 10 days. The differences in PE incidence and the time when it developed in NHF versus THR and TKR patients suggest that these patients should be considered separately when determining the optimal thromboprophylactic regimen.

The prevention of pulmonary embolism (PE) is a main reason for giving thromboprophylaxis to surgical patients. The guidelines for preventing venous thromboembolism recommend anticoagulant treatment for at least 7–10 days after major orthopedic surgery (Geerts et al. 2001). Although the risk of clinical deep vein thrombosis (DVT) continues for more than a month, little information is available on the natural incidence of postoperative clinical PE in the weeks following major joint surgery, or on the timing of its development in patients given thromboprophylaxis in hospital (White et al. 1998, Dahl et al, 2000).

We assessed the annual incidence of radiologically-confirmed, clinical PE after major joint surgery during a 10-year period of prospective observation, to determine the timing of PE in relation to a 6-month postoperative course. We also wished to determine whether additional knowledge can be obtained about these patients, which could be of value to previously reported cases having radiologically-confirmed DVT.

Patients and methods

Patients

Buskerud Central Hospital, a large hospital in southern Norway, serves a mixed urban and rural population of about 250,000. Patients undergoing orthopedic surgery in this hospital are almost always readmitted to the same hospital in the event of postoperative thromboembolic complica-

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tions. The present study included all patients who underwent total hip replacement (THR), total knee replacement (TKR), or nailed hip fracture (NHF) from 1989 through 1998.

Thromboprophylaxis

The patients received thromboprophylaxis for about 10 days during their initial hospitalization. Subcutaneous injections of low-molecular-weight heparin (LMWH), either dalteparin (Fragmin, Pharmacia Corporation; 5,000 IU) or enoxaparin (Clexane/Lovenox, Aventis Pharma; 40 mg), were given once daily, starting 12 hours before the operation in elective cases and after admission in emergency cases.

Diagnosis

Patients readmitted to the hospital with clinically suspected PE were routinely screened with chest radiography and lung perfusion scintigraphy, followed by ventilation scintigraphy. Spiral computed tomography (CT), introduced in the radiology department in 1996, was also used during the last 2 years of the study. The sensitivity of spiral CT seems to exceed that of high-probability lung scanning, at least for large central emboli that are probably of clinical importance (Rodger and Wells 2001).

Lung perfusion scintigraphy was done after an intravenous injection of 150 MBq ^{99m}Tc-labeled human albumin macroaggregates (Isopharma, Nycomed Amersham). At least 4 projections were taken: anterior, posterior, and left and right posterior obliques. Additional projections (laterals or anterior obliques) were obtained when necessary. Lung ventilation scintigraphy was performed after inhalation of 40 MBq ^{99m}Tc-carbon particles (Technegas), using the same projections as in the perfusion studies. In almost all cases, the gamma camera was an Elscint Apex 409 camera with a low-energy, high-resolution collimator; some of the studies after 1997 were done with an Elscint Helix Dual-head gamma camera, also with low-energy, high-resolution collimators. According to the NEMA specifications, the resolutions of the 2 gamma camera systems are almost identical, indicating equivalent diagnostic sensitivity in routine clinical practice (NEMA 1994). The criteria of Biello (Biello 1987) and of the PIOPED investigators (PIOPED Investigators 1990, Gottschalk et al. 1993, Sostman et al. 1994, Freitas et al. 1995) were used to determine the probability of PE, and only high-probability cases were considered in this study. Patients with concomitant suspected DVT were primarily screened with compression B-mode ultrasonography (Ultrasonograph Hitachi EUB-450, Kashiwa, Japan, and Picker L, 7000 A, Kashiwa, Japan) (Gudmundsen et al. 1990). The deep, superficial, and common femoral veins were examined. If no thrombosis was seen, venography was performed, using the technique described by Rabinov and Paulin (1972).

Statistics

No hypotheses were proposed and tested. Descriptive statistics were used. The annual incidence of PE is given as mean, 95% confidence interval (95% CI) and percentage of the total number of operated patients in each surgical group. The development of PE is given as mean (range) days after surgery.

Results

From 1989 through 1998, 3,954 patients underwent total hip and knee joint replacement and hip fracture nailing in Buskerud Central Hospital (Table 1). Their mean age was 74 (29–90) years, and 75% were female. 122 of the patients were either readmitted with clinically suspected PE or they developed suspected PE during their initial hospitalization. 50 of these suspected cases were confirmed as PE by imaging techniques. Thus, the overall incidence of confirmed PE was 1.3% (95% CI, 0.9–1.6%). The incidence of PE was highest in the hip fracture group (1.5%), as compared to patients undergoing hip replacement (1.1%) or knee replacement (0.8%). In the period from 1989 to 1998, the annual incidence of confirmed PE ranged from 0.4% to 3.4% (Table 2). In these patients, symptomatology of PE was the main finding and the reason for the radiological examination. Only 6 of the 50 patients with confirmed PE had clinically suspected and radiologically-confirmed DVT (Table 2). None of the patients with confirmed PE was known to have an underlying vascular disease or inherited procoagulant disorders.

Table 1. Characteristics of patients developing confirmed PE after undergoing major orthopedic procedures, from 1989–1998

Procedure	No. of patients	Confirmed PE n (%)	Age, years median (range)	Ratio women/men		Days of postoperative hospital stay [a] mean (range)	Time to development of PE mean (range)
				operated on	with PE		
NHF	1907	28 (1.5)	81 (29–90)	3/1	5/1	17 (2–37)	24 (1–173)
THR	1661	19 (1.1)	74 (53–90)	3/1	2/1	16 (8–57)	35 (5–94)
TKR	386	3 (0.8)	81 (53–84)	2/1	All female	24 (9–48)	9 (2–17)

PE pulmonary embolism, NHF nailed hip fracture, THR total hip replacement, TKR total knee replacement
[a] Length of hospitalization data not available for 1 patient with NHF and 3 patients with THR.

Table 2. Annual incidence of readmission for suspected PE after major joint operations

Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	Total
Total operated	261	230	279	396	475	429	456	450	509	469	3954
Suspected PE	18	12	9	12	13	12	17	16	6	7	122
Confirmed PE	9	4	3	6	4	4	8	8	2	2	50
Incidence, %	3.4	1.7	1.1	1.5	0.8	0.9	1.8	1.8	0.4	0.4	1.3 [a]
DVT	0	0	1	0	0	0	2	2	0	1	6

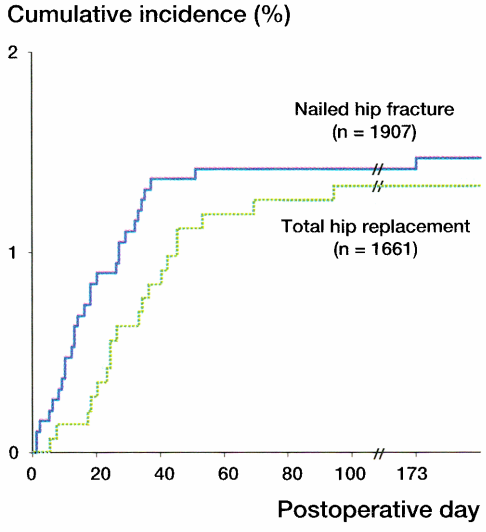
PE pulmonary embolism, DVT deep vein thrombosis
[a] 95% CI: 0.92–1.61%

Table 3. Length of hospitalization and time to development of PE after major orthopedic procedures, from 1989–1998

Procedure	Number of patients	Length of postoperative hospital stay, days mean (range)	Time to development of PE, days mean (range)
NHF			
PE diagnosed during initial hospitalization	13	22 (2–37)	11 (1–27)
PE diagnosed after discharge	14	13 (8–22)	37 (9–173)
Date of discharge missing	1	Not available	18
THR			
PE diagnosed during initial hospitalization	4	32 (17–57)	15 (5–24)
PE diagnosed after discharge	12	11 (8–22)	40 (17–94)
Date of discharge missing	3	Not available	23 (20–26)
TKR			
PE diagnosed during initial hospitalization	2	29 (9–48)	5 (2–7)
PE diagnosed after discharge	1	14	17

PE pulmonary embolism, NHF nailed hip fracture, THR total hip replacement, TKR total knee replacement.

In the combined population, the mean time from surgery to development of PE was 27 (1–173) days. Table 1 shows the length of time after surgery to the development of PE in the various subgroups. Late PE was commonest in patients undergoing THR, with a mean time of 35 days to development. The timing of the PE diagnosis relative to discharge from hospital in the three treatment groups is shown in Table 3. Figure 1 shows the cumulative incidence of PE during the initial 6 postoperative months in patients undergoing THR or NHF surgery. (Since only 3 patients with TKR developed radiologically confirmed, clinical PE, these events were not plotted.)



Cumulative incidence of radiologically-confirmed PE after NHF or THR surgery.

Discussion

Patients undergoing major orthopedic surgery are at increased risk of developing thrombotic complications, and the risk of venous thromboembolism remains high, despite the use of thromboprophylaxis in hospital. We recently did a prospective study concerning the incidence of late-occurring, clinical DVT in joint-operated patients (Dahl et al. 2000). That 9-year study showed an annual incidence of 2.1% (95% CI, 1.6–2.6%) of radiologically-confirmed, symptomatic DVT. The patients readmitted for suspected DVT had no symptoms of concomitant PE. The incidence of radiologically confirmed, clinical PE in our current study—1.3%—combined with the results of the previous study yields an estimated annual incidence of at least 3% of clinical thromboembolism after major joint surgery. In contrast, the expected rate of spontaneous venous thromboembolism in the general population has been estimated at only 0.18% (Oger 2000).

We found no symptoms suggesting concomitant DVT in 88% of the patients with confirmed, PE, which would suggest that the underlying thromboembolic event was subclinical in these cases. Since pulmonary angiography was not performed routinely after inconclusive ventilation-perfusion scanning, it seems likely that some PEs were not diagnosed. Moreover, because our study only recorded radiologically-confirmed, clinical PE, the observed incidence of 1.3% probably underestimates the true number of clinically relevant events. Many fatal PEs occurring after discharge are not detected because of the low rate of autopsy and inaccuracy of death certificates; however, it has been estimated that the incidence of fatal PE after surgery ranges from 0.1% to 0.4% in THR and 3.6% to 12.9% in NHF (Geerts et al. 2001). Other large-scale epidemiological studies have indicated that major joint-operated patients have a higher mortality rate for more than 2 months after surgery, mainly due to vascular complications (Frostick 2000, Lie et al. 2000).

Patients diagnosed with PE in this study were not known to have procoagulant conditions predisposing them to venous thromboembolism; thus, these late-occurring episodes are assumed to be related to the surgery. In a previous study, activated protein C resistance was not found in a higher frequency after hip surgery than in the normal population. This supports the view that congenital procoagulant conditions do not play a dominant role in the pathogenesis of these late-occurring events following major orthopedic surgery (Sandset et al. 1999).

Studies of patients who underwent THR have indicated that extending anticoagulant prophylaxis with LMWH to 4–5 weeks postoperatively significantly reduces the incidence of venographically-detected DVT, as compared to a regimen of only 1–2 weeks (Bergqvist et al. 1996, Planes et al. 1996, Dahl et al. 1997, Lassen et al. 1998, Hull et al. 2000, Comp et al. 2001). Three recent meta-analyses have shown a relative reduction in venographically-proven subclinical DVT that parallels a similar reduction in postoperative clinical thromboembolic events (Cohen et al. 2001, Eikelboom et al. 2001, Hull et al. 2001). Our findings confirmed that the risk of clinical PE and DVT extends beyond the usual hospitalization period in patients receiving prophylaxis for a few days, suggesting that the times taken to develop clinical DVT and PE are similar. In our previous study, the average time to development of symptomatic DVT was 27 days after THR, 36 days after NHF, and 16 days after TKR. These times resemble those we found in almost the same surgical population for

development of PE (35 days after hip replacement, 24 days after a hip fracture, and 9 days after knee replacement). The time from surgery to development of PE (patients developing PE in hospital) or discharge (patients developing late PE) was similar (Table 3).

Our findings suggest that the time to development of a thromboembolism after joint surgery may depend on the type of surgery performed, and therefore different antithrombotic regimens may be necessary. The risk of PE was greatest after NHF, with 9/28 events occurring within 10 days of surgery. More intensive prophylaxis may be needed for these patients—many of them older—who do not receive antithrombotic medication until hours after the primary trauma. In contrast, the time to development of PE was longest in the group undergoing THR, with an average time to readmission of 35 days. As shown in the Figure, patients undergoing THR appear to be at increased risk for about 12 weeks after surgery, as compared to 6–7 weeks after NHF. The time to PE for patients undergoing knee replacement was the shortest in the three groups, with a mean of 9 days. Although the number of patients undergoing TKR was too few to draw firm conclusions, our results accord with those of White et al. (1998) who found that venous thromboembolism developed after discharge in 76% of THR, versus 47% of TKR. In the latter study, the incidence of venous thromboembolism after TKR was highest soon after surgery and stabilized after 3–4 weeks; but after THR, the incidence of thromboembolic events increased more slowly and stabilized about 10–12 weeks after surgery. This difference emphasizes that the pathophysiological pattern differs in each group of patients, which is in accordance with vascular flow studies in various groups of orthopedic patients (McNally et al. 1997). Such views also agree with a recent study showing that extending prophylaxis with the same dosage of a LMWH, enoxaparin, to 1 month significantly reduced the occurrence of venous thromboembolism in patients undergoing THR, but not in patients undergoing knee replacement, indicating a different response to the same prophylactic regimen (Comp et al. 2001). The optimal dosage and the timing of prophylaxis relative to surgery may differ in these 2 groups of patients, and more investigations are needed.

In this study, several patients had PE soon after their procedure. This is in line with previous findings that major orthopedic surgery induces a marked hypercoagulable state both locally—in veins draining the surgical site—and in the lungs, which are the primary target organ for procoagulant debris embolized from the bone marrow (Dahl et al. 1993, 1995). We found that patients who underwent operations for hip fractures were particularly prone to the development of early PE. Thus, timing in relation to surgery, dosage (vide supra), and duration of prophylaxis seem to be important and open questions concerning all homogeneous groups of orthopedic patients if one is to obtain effective prevention of thrombus formation and progression without increasing bleeding (Dahl 1997).

In view of the risk of early venous thromboembolism, the practice of deferring anticoagulation until after surgery, as done by some anesthesiologists for fear of bleeding and paraplegia after locoregional analgesia, may be questioned, since this complication occurs extremely seldom and is probably multi-etiological at least with the low-molecular-weight dosages recommended in Europe (Dahl 2000).

Taken together, our findings show that patients undergoing major joint surgery and, in particular, hip surgery, are at risk of radiologically confirmed, clinical PE shortly after surgery and for many weeks even thereafter, when prophylaxis is given for only a few days. The pattern of clinical appearance of PE differs in heterogeneous orthopedic groups. More studies are needed to determine the optimal prophylaxis. Dosage, timing of initiation in relation to surgery, and duration of prophylaxis are important matters for all homogeneous groups of orthopedic patients. Individual prophylaxis should be the goal of future research.

No competing interests declared.

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