Clin Orthop Relat Res (2010) 468:115–119
DOI 10.1007/s11999-009-1020-6

SYMPOSIUM: PAPERS PRESENTED AT THE ANNUAL MEETINGS OF THE KNEE SOCIETY

# High Incidence of Complications From Enoxaparin Treatment After Arthroplasty

**Andrew S. Neviaser MD, Charles Chang MD,
Stephen Lyman PhD, Alejandro Gonzales Della Valle MD,
Steven B. Haas MD**

Published online: 11 August 2009


**Abstract** Pulmonary embolism (PE) complicates 1% to 10% of total joint arthroplasties and generally requires immediate anticoagulation. Low-molecular-weight heparins have supplanted unfractionated heparin as the treatment of choice for PE and hold a 1A recommendation from the American College of Chest Physicians for this indication. However, the complications of enoxaparin treatment begun in close proximity to arthroplasty surgery are not well described. We examined the records of 135 patients who underwent total joint arthroplasty, experienced an in-hospital PE, and received treatment with enoxaparin at therapeutic doses (1 mg/kg body weight). The type and frequency of complications were determined and classified as major or minor. Twenty-seven percent of patients experienced minor complications and 10% experienced major complications. The incidence of major bleeding was substantially higher than rates reported for nonsurgical patients. The overall complication rate of enoxaparin treatment is similar to the rate of complications reported for unfractionated heparin treatment in this setting, but the complications are less severe.
**Level of Evidence:** Level IV, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
This work was performed at the Hospital for Special Surgery.

A. S. Neviaser (✉), S. Lyman, A. Gonzales Della Valle, S. B. Haas
Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA
e-mail: neviasera@hss.edu

C. Chang
Weill Cornell Medical College, New York, NY, USA

## Introduction

Pulmonary embolism (PE) complicates 1% to 10% of total joint arthroplasties and generally requires immediate anticoagulation [8, 23, 24, 27, 28]. Because the risk of developing PE is greatest in close proximity to surgery, the treating surgeon is faced with starting aggressive, potent anticoagulation at a time when the risk of bleeding from the surgical site is highest [12]. Major surgical site bleeding increases the risk of neurologic damage [4, 5] and reoperation [7], delays recovery [16, 25], and increases the risk of infection by 12.3% [31]. Potentially fatal bleeding can also occur in other organ systems [19, 29]. Treatment should balance the benefits and risks of anticoagulation in patients who have recently undergone these procedures.

Intravenous unfractionated heparin (UFH) is the traditional treatment for PE in nonsurgical patients [8]. In patients who have had total joint arthroplasty, the risk of major bleeding with UFH treatment is high, ranging from 9% to 47% [13, 18, 26]. Low-molecular-weight heparins (LMWHs) have replaced UFH for many clinical indications, including the treatment of PEs [8]. They have more specific binding affinities and, as a result, have more predictable pharmacokinetic and pharmacodynamic properties than UFH [9]. LMWHs can be administered subcutaneously, do not require laboratory monitoring, and are equally as effective as UFH [8]. The safety of LMWHs in postoperative orthopaedic patients has been the subject of

much controversy [3, 6, 33]. To our knowledge, all studies conducted in patients undergoing arthroplasty to date have examined their use at lower prophylactic dosing rather than higher therapeutic doses. Enoxaparin is a commonly used LMWH and is an effective prophylactic agent [13]. We are unaware of a study demonstrating that enoxaparin is safe when used at therapeutic doses (1 mg/kg of body weight) in the early postoperative period after total joint arthroplasty.

Our purposes were, therefore, (1) to delineate the type and incidence of complications associated with the use of enoxaparin at therapeutic doses in close proximity to total joint arthroplasty; and (2) to identify risk factors associated with complications.

## Patients and Methods

After approval from the Institutional Review Board, we searched the hospital records of all 14,984 TKAs and THAs performed at our institution from 2003 to 2005. Hospital records were searched for patients receiving Current Procedural Terminology codes 27447 (TKA), 27487 (revision TKA), 27130 (THA), and 27134 (revision THA). This group of patients was then searched for International Classification of Diseases, Ninth Revision codes 415.1 (pulmonary embolism not iatrogenic), 415.11 (pulmonary embolism-iatrogenic), and 451.19 (other pulmonary embolism and infarction). Patients were included in this study if they met the following criteria: (1) underwent primary or revision THA or TKA; (2) had a PE during their postoperative hospital stay; and (3) were treated with therapeutic doses of enoxaparin within the first 10 postoperative days. Therapeutic dosing of enoxaparin included 1 mg/kg of body weight administered subcutaneously twice per day or if a patient weighed more than 60 kg, a minimum of 60 mg twice per day was required. The presence of PE was established by spiral computed tomography or ventilation-perfusion (V/Q) scan, which were obtained if clinical symptoms warranted. No type of screening for thromboembolism was performed [14]. Patients were excluded if they had impaired renal function, defined as a creatinine of 1.6 mg/dL or greater, or if they had a history of hepatic dysfunction before surgery.

One hundred thirty-five patients (152 procedures) met inclusion criteria (92 primary TKAs, 55 primary THAs, five revision TKAs). There were 78 female and 57 male patients. The average age was 69.7 years (range, 30–88 years). All patients received a multimodal thromboprophylaxis protocol consisting of stopping procoagulant medication before surgery, preoperative donation of

**Table 1.** Comorbidities of patients treated with enoxaparin

| Category | Number of patients |
|---|---|
| Cardiovascular | |
| Hypertension | 76 |
| Hypercholesterolemia | 46 |
| Coronary artery disease | 16 |
| Mitral valve prolapse | 5 |
| Cardiac murmur | 5 |
| Atrial fibrillation | 8 |
| Other | 32 |
| Gastrointestinal | |
| Gastrointestinal reflux disease | 33 |
| Peptic ulcer disease | 6 |
| Cholelithiasis | 3 |
| Other | 17 |
| Genitourinary | |
| Benign prostatic hypertrophy | 13 |
| Nocturia | 3 |
| Other | 9 |
| Endocrine | |
| Diabetes mellitus | 34 |
| Hypothyroid | 11 |
| Hematology/oncology | |
| Cancer | 15 |
| Deep vein thrombosis | 7 |
| Anemia | 3 |
| Infectious disease | |
| Hepatitis B | 2 |
| HIV | 1 |
| Other | 3 |
| Musculoskeletal | |
| Osteoarthritis | 11 |
| Osteoporosis | 10 |
| Spinal stenosis | 4 |
| Gout | 4 |
| Sciatica | 3 |
| Other | 20 |
| Neurological | |
| Vertigo | 2 |
| Migraines | 2 |
| Syncope | 2 |
| Other | 2 |
| Ophthalmologic | |
| Glaucoma | 5 |
| Other | 4 |
| Psychiatric | |
| Depression | 5 |
| Other | 5 |

**Table 1.** continued

| Category | Number of patients |
|---|---|
| Renal | |
| Chronic renal insufficiency | 1 |
| Other | 3 |
| Respiratory | |
| Asthma | 21 |
| Pneumonia | 3 |
| Other | 9 |

autologous blood, use of regional anesthesia [34], pneumatic compression devices [10], rapid mobilization postoperatively, and early foot and ankle flexion-extension exercises [30]. In addition, they received pharmacologic thromboprophylaxis with aspirin (325 mg twice a day in 21 patients) or warfarin (5 mg administered on the night of the day of surgery and daily thereafter, aiming at an international normalized ratio of 2, in 114 patients) [1]. Patients had an average of 3.4 comorbidities (Table 1). The mean BMI was 30.9 kg/m$^2$ (range, 15.5–56.5 kg/m$^2$). Diagnosis and treatment of PE began, on average, 3.1 days after surgery (range, 1–8 days). All diagnoses of PE were made by computed tomography [17], except in one patient who had a high-probability V/Q scan. The average twice-daily dosing of the enoxaparin was 78.3 mg (range, 40–130 mg). All patients were started (or continued) on oral warfarin therapy at the time of diagnosis and were treated with enoxaparin until their international normalized ratio reached a stable level between 2 and 3. Criteria for the diagnosis of complications were those used by Patterson et al. associated with the use of unfractionated heparin [26]. These were (1) hemorrhage at the operative site, defined by formation of a clinically evident hematoma (clinical determination of hematoma included documented presence of edema, ecchymosis, and serosanguinous wound drainage) or decrease in hematocrit of more than 5% requiring transfusion; (2) hemorrhage at a nonoperative site, ie, spontaneous hemorrhage unrelated to the location of surgery; (3) thrombocytopenia, defined by a drop in the platelet count to less than 100,000/mm3 or a decrease of more that 200,000/mm3; and (4) recurrent PE or arterial thrombosis. Complications defined as major included recurrent PE or arterial thrombosis; fatal hemorrhage; hemorrhage that was retroperitoneal, intracranial, or intraspinal; hemorrhage leading to reoperation or cessation of anticoagulation treatment; and overt hemorrhage requiring two or more units of blood transfusion [11]. Those complications that did not meet these criteria were considered minor.

We used a logistic regression model to identify predictors of complication (age, gender, BMI, primary/revision surgery, hip or knee arthroplasty, unilateral or bilateral procedure, dose of enoxaparin, prophylactic use of aspirin or warfarin prophylaxis, and number of comorbidities as potential predictors of complication).

**Table 2.** Complications of enoxaparin treatment after arthroplasty

| Complication | Major | Minor |
|---|---|---|
| Operative site hemorrhage | 12 patients | 31 patients |
| Nonoperative site hemorrhage | 1 patient | 7 patients |
| Thrombocytopenia | 0 | — |
| Recurrent pulmonary embolus | 0 | — |
| Mortality | 0 | — |

## Results

Fifty-one complications occurred in 45 patients (33%) (Table 2). There were 13 major (10%) and 38 minor (27%) complications. The average international normalized ratio at the time of complication was 1.61 (0.97-3.09). Forty three patients (32%) had operative site hemorrhage, which was the most frequent complication. Eleven (8%) of these were major bleeding requiring two or more units of blood. On average, patients with operative site hemorrhage required 1.5 units. One patient developed a deep wound hematoma with concomitant sciatic nerve compression requiring operative evacuation. This was the only patient who required reoperation. Eight patients (6%) had bleeding at distant sites; one had epistaxis, six had hematuria, and one had a subdural hematoma sustained in a fall. None of the eight patients required blood transfusions for these complications. Anticoagulation treatment was stopped in the patient who had the subdural hematoma, and an inferior vena cava filter was placed. No other complications were recorded. No thrombocytopenia or fatal pulmonary emboli occurred.

Age, gender, BMI, primary/revision surgery, hip or knee arthroplasty, unilateral or bilateral procedure, dose of enoxaparin, and number of comorbidities were not predictive of overall, major, or minor complications. We found no relationship between the postoperative day on which treatment began and the likelihood of bleeding complications. The overall risk of complications was similar for patients who had taken warfarin and those who had taken aspirin for prophylaxis.

## Discussion

The incidence of in-hospital PE after total joint arthroplasty has remained steady in the last decade [21, 23]. Treatment

of this complication presents the arthroplasty surgeon with a dilemma. Anticoagulation in postoperative patients carries obvious risks. However, the need for treatment of PEs, and the reduction in mortality that this treatment affords, has been definitively established [2, 3, 15]. LMWHs have supplanted UFH as the treatment of choice for PE and hold a 1A recommendation from the American College of Chest Physicians for this indication [8]. However, lower prophylactic doses of enoxaparin have been associated with higher rates of wound drainage and reoperation than aspirin or warfarin prophylaxis [3]. The complication rate of therapeutic enoxaparin treatment in the patients undergoing arthroplasty in the early postoperative period has not previously been established. Understanding the risk profile is essential for weighing the risks and benefits of this treatment. The purposes of this study were (1) to delineate the type and incidence of complications associated with the use of enoxaparin at therapeutic doses in close proximity to total joint arthroplasty; and (2) to identify risk factors associated with complications.

The main limitation of this study is lack of a control group that did not receive anticoagulation. The absence of such a control makes direct attribution of complications to the individual treatments less accurate. However, withholding treatment from patients who have had a PE to create a control group would be unethical. Comparison of the cohort in this study to a group without PE would not be appropriate either. Interventions such as blood transfusions are undertaken with different considerations in patients who sustain the cardiovascular stress of a PE. Thus, one could not accurately compare patients without a PE with those with a PE and its associated cardiovascular stress, because treatment would be considerably affected by this variable [19].

In this cohort of postarthroplasty patients, the incidence of major bleeding complications (10%) was substantially higher than the rates reported for nonsurgical patients, which are 0% to 5% [5, 20, 22, 35]. This difference highlights the unique risks inherent to anticoagulation treatment in patients who have undergone procedures, which include substantial soft tissue dissection and osteotomies. The overall complication rate of enoxaparin treatment is similar to the rate of complications reported for UFH treatment in this setting [18, 26]. However, complications associated with enoxaparin tend to be less severe. In 1989, Patterson et al. reported complications in 35% of postarthroplasty patients treated with UFH from our institution [26]. Forty-one of their 112 patients had anticoagulation stopped as a result of the severity of complications. Only one patient in our cohort required therapy to be stopped. On average, patients treated with enoxaparin had a lower transfusion requirement (by 50%) than those reported for UFH (average 3 versus 1.5 units, respectively). Only one patient treated with enoxaparin required reoperation compared with three patients reported for UFH. Although formal statistical comparisons are unlikely to be valid between two groups treated more than 20 years apart, there appear to be fewer bleeding complications with enoxaparin treatment in patients undergoing modern arthroplasty compared with historic reports of UFH treatment. Surgical site complications, which include wound hemorrhage, have been the most frequently reported complication of enoxaparin prophylaxis [3] and is the most common complication of therapeutic treatment. Although the majority of these are minor, 8% of patients in the current study had major surgical site bleeding.

Obesity has been identified as a risk factor for surgical site complications with enoxaparin prophylaxis [3]. We did not find that increased BMI correlated with increased risk for any type of complication. Remarkably, increasing dosage of enoxaparin (which would correlate with increased BMI in weight-based dosing) was also not predictive of complications. Shaieb et al. have reported increased complications when prophylactic enoxaparin was begun within 6 hours of surgery and when used in patients undergoing bilateral procedures [32]. Patterson et al. noted a considerable increase in complications when UFH anticoagulation was begun within the first 5 postoperative days [26]. We found no correlation between the time at which treatment was initiated relative to surgery and subsequent complications. Nor were patients who underwent bilateral procedures more likely to have a complication. Complications were equally likely in patients who underwent hip versus knee arthroplasty.

Our study elucidates the complications associated with modern anticoagulation treatment of perioperative PE after major total joint arthroplasty. Therapeutic enoxaparin treatment postoperatively in patients undergoing arthroplasty has a 10% rate of major bleeding complications and a 27% rate of minor complications. Major bleeding complications occur twice as frequently as reported in nonsurgical patients. Complications of enoxaparin tend to be less severe than those associated with intravenous UFH. Obese patients undergoing arthroplasty who receive high doses of enoxaparin are not at greater risk for complications than patients with lower BMIs, and the risk profile is not different for patients who undergo bilateral procedures.

**Acknowledgments** We thank Brett Lenart, MD, and Michael Loeven, BS, for their assistance with data collection.

## References

1. Asnis PD, Gardner MJ, Ranawat A, Leitzes AH, Peterson MG, Bass AR. The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. *J Arthroplasty.* 2007;22:213–218.

2. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet.* 1960;1:1309–1312.
3. Burnett RS, Clohisy JC, Wright RW, McDonald DJ, Shively RA, Givens SA, Barrack RL. Failure of the American College of Chest Physicians-1A protocol for lovenox in clinical outcomes for thromboembolic prophylaxis. *J Arthroplasty.* 2007;22:317–324.
4. Butt AJ, McCarthy T, Kelly IP, Glynn T, McCoy G. Sciatic nerve palsy secondary to postoperative haematoma in primary total hip replacement. *J Bone Joint Surg Br.* 2005;87:1465–1467.
5. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, Laporte S, Faivre R, Charbonnier B, Barral FG, Huet Y, Simonneau G. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med.* 1998;338:409–415.
6. Eriksson BI, Friedman RJ, Cushner FD, Lassen MR. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res.* 2008;466:2009–2011; author reply 2012–2014.
7. Galat DD, McGovern SC, Hanssen AD, Larson DR, Harrington JR, Clarke HD. Early return to surgery for evacuation of a postoperative hematoma after primary total knee arthroplasty. *J Bone Joint Surg Am.* 2008;90:2331–2336.
8. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW, American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest.* 2008;133:381S–453S.
9. Goodman LS, Gilman A, Brunton LL, Lazo JS, Parker KL. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 11th Ed. New York, NY: McGraw-Hill; 2006.
10. Haas SB, Insall JN, Scuderi GR, Windsor RE, Ghelman B. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg Am.* 1990;72:27–31.
11. Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, McLoughlin D, Armstrong P. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med.* 1979;301:855–858.
12. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, Holmqvist A, Mant M, Dear R, Baylis B, Mah A, Brant R. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial investigators. *Arch Intern Med.* 2000;160:2199–2207.
13. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA.* 1994;271:1780–1785.
14. Iorio R, Dhupar S, Healy WL, Wong E. Routine duplex ultrasound screening after TKA is not necessary. *Clin Orthop Relat Res.* 2006;452:171–174.
15. Kanis JA. Heparin in the treatment of pulmonary thromboembolism. *Thromb Diath Haemorrh.* 1974;32:519–527.
16. Keays AC, Mason M, Keays SL, Newcombe PA. The effect of anticoagulation on the restoration of range of motion after total knee arthroplasty: enoxaparin versus aspirin. *J Arthroplasty.* 2003;18:180–185.
17. Kim HJ, Walcott-Sapp S, Leggett K, Bass A, Adler RS, Pavlov H, Westrich GH. The use of spiral computed tomography scans for the detection of pulmonary embolism. *J Arthroplasty.* 2008;23:31–35.
18. Lawton RL, Morrey BF. The use of heparin in patients in whom a pulmonary embolism is suspected after total hip arthroplasty. *J Bone Joint Surg Am.* 1999;81:1063–1072.
19. Lee MC, Nickisch F, Limbird RS. Massive retroperitoneal hematoma during enoxaparin treatment of pulmonary embolism after primary total hip arthroplasty: case reports and review of the literature. *J Arthroplasty.* 2006;21:1209–1214.
20. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med.* 1996;334:677–681.
21. Liu SS, Della Valle AG, Besculides MC, Gaber LK, Memtsoudis SG. Trends in mortality, complications, and demographics for primary hip arthroplasty in the United States. *Int Orthop.* 2009;33:643–651.
22. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, Elias D, Grigg A, Musset D, Rodgers GM, Trowbridge AA, Yusen RD, Zawilska K, Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med.* 2001;134:191–202.
23. Parvizi J, Azzam K, Rothman RH. Deep venous thrombosis prophylaxis for total joint arthroplasty: American Academy of Orthopaedic Surgeons guidelines. *J Arthroplasty.* 2008;23:2–5.
24. Parvizi J, Smith EB, Pulido L, Mamelak J, Morrison WB, Purtill JJ, Rothman RH. The rise in the incidence of pulmonary embolus after joint arthroplasty: is modern imaging to blame? *Clin Orthop Relat Res.* 2007;463:107–113.
25. Patel VP, Walsh M, Sehgal B, Preston C, DeWal H, Di Cesare PE. Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. *J Bone Joint Surg Am.* 2007;89:33–38.
26. Patterson BM, Marchand R, Ranawat C. Complications of heparin therapy after total joint arthroplasty. *J Bone Joint Surg Am.* 1989;71:1130–1134.
27. Phillips CB, Barrett JA, Losina E, Mahomed NN, Lingard EA, Guadagnoli E, Baron JA, Harris WH, Poss R, Katz JN. Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. *J Bone Joint Surg Am.* 2003;85:20–26.
28. Pulido L, Parvizi J, Macgibeny M, Sharkey PF, Purtill JJ, Rothman RH, Hozack WJ. In hospital complications after total joint arthroplasty. *J Arthroplasty.* 2008;23:139–145.
29. Ries MD, Guiney W Jr, Lynch F. Fatal massive adrenal hemorrhage after bilateral total knee arthroplasty. *J Arthroplasty.* 1994;9:559–562.
30. Salvati EA, Sharrock NE, Westrich G, Potter HG, Valle AG, Sculco TP. The 2007 ABJS Nicolas Andry Award: three decades of clinical, basic, and applied research on thromboembolic disease after THA: rationale and clinical results of a multimodal prophylaxis protocol. *Clin Orthop Relat Res.* 2007;459:246–254.
31. Sanchez-Ballester J, Smith M, Hassan K, Kershaw S, Elsworth CS, Jacobs L. Wound infection in the management of hip fractures: a comparison between low-molecular weight heparin and mechanical prophylaxis. *Acta Orthop Belg.* 2005;71:55–59.
32. Shaieb MD, Watson BN, Atkinson RE. Bleeding complications with enoxaparin for deep venous thrombosis prophylaxis. *J Arthroplasty.* 1999;14:432–438.
33. Sharrock NE, Gonzalez Della Valle A, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res.* 2008;466:714–721.
34. Sharrock NE, Haas SB, Hargett MJ, Urquhart B, Insall JN, Scuderi G. Effects of epidural anesthesia on the incidence of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg Am.* 1991;73:502–506.
35. Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, Sie P, Silsiguen M, Combe S. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med.* 1993;153:1541–1546.