Evaluation of the Safety and Efficacy of Enoxaparin and Warfarin for Prevention of Deep Vein Thrombosis After Total Knee Arthroplasty

Steven H. Stern, MD, Richard L. Wixson, MD, and Daryl O’Connor, MD

Abstract: Of 263 patients who underwent total knee arthroplasty, 122 received adjusted low-dose warfarin and 141 received enoxaparin as deep vein thrombosis (DVT) prophylaxis. Three patients in the warfarin group and 3 in the enoxaparin group developed ultrasound-detectable DVT (P > .05). Although the amount of perioperative blood transfused was equivalent in both groups, the overall hemoglobin drop was greater (P < .005) in the enoxaparin group (2.9 g/dL) as compared with the warfarin group (2.3 g/dL). Five patients (4.6%) in the warfarin group and 16 (11.3%) in the enoxaparin group had bleeding complications (P < .05). Our data support earlier published reports suggesting that reductions, if any, in the incidence of DVT associated with enoxaparin are offset by a significant increase in bleeding complications as compared with adjusted-dose warfarin. We continue to use adjusted-dose warfarin as primary thromboembolic prophylaxis after total knee arthroplasty. Key words: enoxaparin, knee arthroplasty, deep vein thrombosis prophylaxis, warfarin.

A new form of deep venous thrombosis (DVT) prophylaxis became available in the United States when the U.S. Food and Drug Administration approved the use of enoxaparin, a low–molecular weight heparin, for use after total joint arthroplasty [1–3]. Low–molecular weight heparin offered several conceptual advantages over other pharmacologic DVT prophylaxis methods. Theoretically, low–molecular weight heparin does not require routine monitoring, can be administered in identical doses for all patients, and requires a shorter period of anticoagulation therapy [3]. Numerous reports have been published on the results of low–molecular weight heparin when used as a DVT prophylaxis agent after total knee arthroplasty (TKA) [4–10]. When enoxaparin was used in routine clinical practice at our institution, the surgeons noted increased wound drainage, bleeding, and leg swelling. These increased bleeding complications were believed to be significant and led to a return to use of adjusted-dose warfarin for pharmacologic DVT prophylaxis after TKA. We hypothesized that although enoxaparin was as efficacious as adjusted-dose warfarin in preventing thrombosis formation, its use also resulted in an increased incidence of bleeding.

Materials and Methods

Patient Population

From 1990 to 1996, 271 patients underwent consecutive index TKAs under the care of 2 senior surgeons (R.L.W. and S.H.S.). All procedures were done at a tertiary care teaching institution. For the purpose of this retrospective study, inclusion criteria were primary TKA use of either enoxaparin or...
adjusted-dose warfarin as thromboembolic prophylaxis. Eight patients were excluded because of use of another method of prophylaxis. Of 263 patients included, 141 received enoxaparin, and 122 received adjusted-dose warfarin. These 2 groups were not randomized. The preferred prophylaxis protocol at our institution was adjusted-dose warfarin during 1990 to 1992 and enoxaparin from 1993 to 1996. There was no statistical significant difference in the demographics between the 2 groups (Table 1). More patients received regional anesthesia in the enoxaparin group than in the adjusted-dose warfarin group (26% vs 8%). This difference reflected the changing practice of our anesthesia department.

Thromboembolic Prophylaxis

Adjusted-dose warfarin prophylaxis consisted of an initial 5-mg dose, followed by an adjusted-dose regimen with the goal being to maintain the prothrombin time at approximately 1.5 to 2.0 times control. Adjusted-dose warfarin anticoagulation prophylaxis was continued for 4 to 6 weeks postoperatively, with biweekly blood checks and dose adjustment to maintain the appropriate prothrombin time level. Patients receiving fixed-dose enoxaparin received 30 mg subcutaneously twice a day. The average time interval between the end of surgery and first enoxaparin dose was 16 hours (standard deviation [SD], 9 hours). Enoxaparin prophylaxis was routinely continued for 2 weeks. No routine laboratory monitoring was used in the patients receiving enoxaparin therapy. No further pharmacologic methods were used after the enoxaparin or the adjusted-dose warfarin course was completed. All patients successfully completed the recommended length of prophylaxis. In addition to the pharmacologic anticoagulation listed, patients were routinely treated with antiembolism stockings and compression foot pumps.

Outcome Measures

Clinical efficacy was determined by the frequency of documented DVT or symptomatic pulmonary embolism. At the time under study in this report, routine duplex Doppler ultrasound studies were performed as part of our institution's protocol on the 4th or 5th postoperative day. All studies were performed by 1 of several specially trained Doppler technicians at our institution. Of the patients analyzed in this report, 95% (249 of 263 patients) successfully completed the postoperative venous Doppler ultrasound study. Patients were considered to have developed DVT if the Doppler ultrasound examination revealed significant noncompressible vein segments [11].

Clinical safety was determined by the amount of blood loss during the hospitalization. Clinically significant bleeding episodes were defined as any postoperative bleeding event documented in the patient's medical record. Major bleeding was defined as i) any documented overt bleeding event that decreased hemoglobin levels by 2 g/dL in 1 24-hour period, excluding the first 24 hours postoperatively, or ii) hemarthrosis requiring discontinuation of prophylaxis for at least 24 hours. Minor bleeds were events documented in the medical record (ie, wound drainage or bleeding at other sites) that did not reach the criteria for major bleeds. A mean blood loss index was calculated for all patients to obtain a more objective measure of bleeding. The blood loss index by convention is defined as the sum of the difference between the patient's preoperative and discharge hemoglobin levels added to the number of units of blood transfused [10].

Statistical Analysis

The rates of DVT and wound or bleeding complications in the 2 groups were compared using the

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
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<tr>
<td>No. patients</td>
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<td>Male</td>
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</tr>
<tr>
<td>Epidural</td>
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<tr>
<td>Spinal</td>
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</tbody>
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*Trade name for low–molecular weight heparin.
chi-square test with Fisher’s exact test. Blood loss, time intervals, and other baseline patient demographic data were compared using Student’s t-test for independent samples.

**Results**

**Incidence of Deep Vein Thrombosis**

Objective testing (venous ultrasound) was available in 93% of patients (113 of 122) in the adjusted-dose warfarin group and 96% of patients (136 of 141) in the enoxaparin group. Venous ultrasound confirmed the presence of DVT in 3 of 113 patients (2.7%) who received adjusted-dose warfarin and 3 of 136 patients (2.2%) who received enoxaparin (Table 2). Proximal DVT occurred in 1 patient in the adjusted-dose warfarin group and 2 patients in the enoxaparin group. Although bilateral venous ultrasonography was performed on all patients, all of the detected occurrences of DVT were isolated to the operative extremity.

**Incidence of Bleeding Complications**

Clinically significant major bleeds were seen in 2 patients in the enoxaparin group as compared with 1 patient in the adjusted-dose warfarin group. Minor bleeding complications were noted in 14 patients in the enoxaparin group as compared with 4 in the adjusted-dose warfarin group. The overall bleeding rate was statistically higher in the patients receiving enoxaparin prophylaxis (11.3% vs 4.1%) compared with patients receiving adjusted-dose warfarin anticoagulation ($P < .05$) (Table 2). Of the 64 patients who received enoxaparin within the first 12 hours of surgery, 6 manifested episodes of overt bleeding (9%) as compared with 10 overt bleeds in the 77 patients (13%) whose initial dose of enoxaparin was >12 hours after surgery (not significant).

The average reduction in hemoglobin levels from presurgical levels to discharge studies was 2.9 g/dL (SD, 1.6) in the enoxaparin group and 2.3 g/dL (SD, 1.4) in the adjusted-dose warfarin group. The amount of perioperative blood transfused was equivalent in both treatment groups (average 2.1 units in both groups). The mean blood loss index was 4.7 (SD, 1.7) in the enoxaparin group as compared with 4.1 (SD, 1.7) in the adjusted-dose warfarin group ($P < .02$) (Table 2).

The small number of patients with major bleeding episodes required slightly longer hospital stays, but the long-term clinical outcome in these patients was unaffected. Although the minor bleeding episodes were concerning, they did not result in further surgery, longer hospital stays, or any obvious alteration in clinical outcomes. No patient required hospital readmission for bleeding or thromboembolic complications.

**Discussion**

Multiple studies have examined the efficacy of low–molecular weight heparins by comparing them with placebo [6,7] or intravenous heparin [6,12,13]. Fewer studies have directly compared low–molecular weight heparins with adjusted-dose warfarin for use after TKA. In general, these studies have reported that low–molecular weight heparins were efficacious in reducing the incidence of DVP, but this may be at the expense of increased bleeding or wound complications [5,10,14,15].

Leclerc et al. [8] compared the effectiveness and safety of fixed-dose enoxaparin and adjusted-dose warfarin after TKA. These authors found 51.7% (109 of 211) of the adjusted-dose warfarin recipients had DVT as compared with 36.9% (76 of 206) of the enoxaparin patients ($P = .003$). The incidence of the more significant proximal clots (approximately 10%) was almost identical in the 2 groups. The incidence of major and minor bleeding was 26.6% in the adjusted-dose warfarin group as compared with 30.1% in the enoxaparin group.

Hull et al. [5] reported on another large series of patients comparing the efficacy of adjusted-dose warfarin and fixed-dose, low–molecular weight heparin (Logiparin, Novo Nordisk, Bagsvaerd, Denmark). In this double-blind, randomized report, the incidence of DVP diagnosed by venography was

<table>
<thead>
<tr>
<th>Table 2. Results</th>
<th>Warfarin</th>
<th>Lovenox*</th>
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<tr>
<td>No. patients</td>
<td>122</td>
<td>141</td>
<td>263</td>
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<tr>
<td>No. Doppler</td>
<td>113</td>
<td>136</td>
<td>249</td>
</tr>
<tr>
<td>No. DVT (%)</td>
<td>3 (2.7%)</td>
<td>3 (2.2%)</td>
<td>6 (2.4%)</td>
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<tr>
<td>Bleeding Minor</td>
<td>4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Major</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>5 (4.1%)</td>
<td>16 (11.3%)</td>
<td>21 (8.0%)†</td>
</tr>
<tr>
<td>Blood loss index</td>
<td>12.6 ± 1.4</td>
<td>13.0 ± 1.3</td>
<td>12.8 ± 1.4</td>
</tr>
<tr>
<td>Preoperative Hgb</td>
<td>10.4 ± 1.2</td>
<td>10.2 ± 1.2</td>
<td>10.3 ± 1.2</td>
</tr>
<tr>
<td>Hgb drop</td>
<td>2.3 ± 1.4</td>
<td>2.9 ± 1.6</td>
<td>2.6 ± 1.6</td>
</tr>
<tr>
<td>Units transfused</td>
<td>2.1 ± .9</td>
<td>2.1 ± .8</td>
<td>2.1 ± .9</td>
</tr>
<tr>
<td>(no.)</td>
<td>4.1 ± 1.7</td>
<td>4.7 ± 1.7</td>
<td>4.4 ± 1.7§</td>
</tr>
</tbody>
</table>

*Trade name for low–molecular weight heparin. Manufactured by Aventis Pharmaceuticals Inc., Collegeville, PA.
†$P = .039$.
‡$P = .002$.
§$P = .015$.
DVT, deep venous thrombosis; Hgb, hemoglobin.
54.9% (12.3% for proximal clots) in the adjusted-dose warfarin group as compared with 45.0% (7.8% for proximal clots) in the low-molecular weight heparin group. Patients receiving the low-molecular weight heparin showed a slight increased propensity for bleeds with 2.4% of the patients manifesting bleeds on adjusted-dose warfarin prophylaxis (0.9% major bleeds) as compared with 4.4% (2.8% major bleeds) of the low-molecular weight heparin recipients. Wound hematomas were more common in the low-molecular weight heparin group (8.8%) compared with the adjusted-dose warfarin group (5.9%).

Our data showed no significant difference in the rate of DVT between the enoxaparin (2.2%) and adjusted-dose warfarin (2.7%) groups. The overall rates were considerably lower than in previous studies, however, suggesting either superior anti-coagulation or inferior detection methods at our center. The relatively low rate of DVT may be related to the use of Doppler ultrasound as the detection test mechanism in our series. Many other reports have used venography, which has been shown to be more sensitive than venous ultrasound, as the method to detect thrombosis [11,16–20]. The incidence of proximal DVT was not significantly different between the 2 groups, similar to previous studies that showed no significant difference [5,8,10,14].

The results in the present study showed a significant increased incidence of bleeding and wound complications in the patients receiving enoxaparin. Although many of the differences in the 2 groups were in the increased incidence of minor bleeds, the results did confirm the surgeon’s clinical perception of increased hemorrhage with enoxaparin. The blood loss index was significantly greater in patients receiving enoxaparin. The index has the advantage of attempting to quantify the blood loss associated with surgery. The index does not depend on the subjective views or bias of an observer, which can be especially problematic in examining wounds for drainage or hematoma or in differentiating a minor from a major bleed. Statistically significant differences in the blood loss index (4.7 vs 4.1) between the enoxaparin and adjusted-dose warfarin groups represent a clear quantified measure of increased hemorrhage in the low-molecular weight heparin recipients. Our finding was similar to what was reported in another study comparing the blood loss index in patients receiving adjusted-dose warfarin or ardeparin (RD Heparin) [10].

The present report is retrospective with the known limitations of this method. Prospective reports, however, theoretically have an increased risk of a sentinel effect, in which the study itself causes increased vigilance. In addition, one of the hypothetical benefits of enoxaparin is its ease of use (ie, no monitoring needed, identical doses for all patients) as compared with adjusted-dose warfarin. One would expect the advantages with enoxaparin to be even more pronounced when used in the routine clinical setting. Conversely, adjusted-dose warfarin, which requires monitoring, should benefit from the increased vigilance present in a controlled study. Despite this theoretical advantage, the patients receiving enoxaparin had a similar incidence of DVT and an increased incidence of hemorrhage in this study.

Limitations of the present report include the use of Doppler venous ultrasonography for the detection of DVT. Venography is associated with complications such as pain, allergic reactions, and contrast-related inflammatory responses and is not considered cost-effective for routine screening [21–23]. Doppler ultrasound was routinely used at our institution during the period under review. Ultrasound imaging, however, has been shown to have a lower sensitivity than venography in detecting asymptomatic postoperative DVT [11,16–20]. This previously demonstrated lower sensitivity paired with the low incidence of DVT in our study suggests the possibility of missed asymptomatic DVT. Alternatively, the low incidence of DVT may also be related to the effectiveness of the mechanical prophylaxis measures (foot pumps and thromboembolic disease stockings) employed. The absolute prevalence of DVT in the 2 treatment groups should not be regarded as accurate estimates of the true DVT incidence. Additionally, even though the incidence of thrombosis was similar in the 2 treatment groups, this does not necessarily indicate any difference in efficacy between the 2 drugs. The sample size in our report is not large enough to provide sufficient statistical power to say definitively that there is no difference in efficacy between enoxaparin and adjusted-dose warfarin in terms of DVT prophylaxis [2].

Another limitation of our report is its hospital endpoint with regards to monitoring for postoperative complications. Studies have shown that DVTs continue to occur 3 weeks after surgery [24–29], and bleeding and wound complications can occur throughout the postoperative period. The incidence of DVTs as well as wound and bleeding complications is most likely underestimated. Similarly, the use of a retrospective chart review would also tend to underestimate the true extent of bleeding complications.

Our study supports the recommendation of the fifth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy
that postoperative adjusted-dose warfarin is now a recommended prophylaxis regimen in patients undergoing TKA surgery [30]. This current recommendation is in contrast to the fourth ACCP Consensus Conference on Antithrombotic Therapy, which did not include adjusted-dose warfarin as a recommended prophylaxis regimen [1]. Our data as well as multiple prior reports have revealed a trend toward more bleeding complications with low-molecular-weight heparin. Because optimizing wound healing and minimizing wound bleeding and drainage are of utmost importance in TKA, any medication that compromises the would envelope by subjecting it to increased hemorrhage after TKA must be used with caution. We recognize that many prophylaxis regimens are effective and safe in preventing thromboembolism after TKA. Based on data from this study and others, we continue to use adjusted-dose warfarin as their primary prophylaxis in patients undergoing TKA.

Summary

Our data showed that enoxaparin, administered twice daily after TKA, appears to offer comparable efficacy to adjusted-dose warfarin in terms of ultrasound-detectable DVT prophylaxis. Enoxaparin appeared to be associated with significantly more bleeding complications when compared with adjusted-dose warfarin, however. For this reason, we continue to advocate the use of adjusted-dose warfarin for routine DVT prophylaxis after TKA.

References