ORIGINAL ARTICLE

Acta Orthop Traumatol Turc 2015;49(3):255–259
doi: 10.3944/AOTT.2015.14.0219

Comparison of switch-therapy modalities (enoxaparin to rivaroxaban/dabigatran) and enoxaparin monotherapy after hip and knee replacement

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Objective: Prevention of deep venous thrombosis (DVT) and associated pulmonary embolism following major orthopedic surgeries is challenging, and there is an increased interest in developing new treatment strategies. We compared 2 switch-therapy modalities—enoxaparin to rivaroxaban and enoxaparin to dabigatran—and enoxaparin monotherapy for preventing DVT after total knee arthroplasty (TKA) and total hip arthroplasty (THA).

Methods: This was a prospective, non-blinded, randomized controlled study. We selected 180 eligible patients out of 247 patients undergoing TKA or THA. During the preoperative checkup, patients were randomized to receive either enoxaparin (enoxaparin group) or switch-therapy regimens, comprising enoxaparin during hospitalization and rivaroxaban (rivaroxaban group) or dabigatran (dabigatran group) during the outpatient period. All patients were evaluated for DVT using Doppler ultrasonography (USG) 6 weeks postoperatively. The primary efficacy outcome was the prevention of symptomatic or Doppler ultrasonography (USG)-proven DVT, whereas the primary safety outcome was the incidence of bleeding during the DVT-prophylaxis period.

Results: Doppler USG at 6 weeks after surgery revealed no signs of DVT in any patient. During the hospitalization period, only 2 major bleeding events were reported (1 [1.6%] in the enoxaparin group and 1 [1.6%] in the dabigatran group). No major bleeding events were reported during the outpatient follow-up period in any group. Differences among the 3 groups regarding bleeding events were not statistically significant ($p>0.05$).

Conclusion: When using switch-therapy modalities, clinicians can take advantage of the safety of enoxaparin during the hospitalization period and ease of use of new oral anticoagulant drugs during the outpatient period.

Keywords: Deep venous thromboembolism; new oral anticoagulant drugs; switch therapy.

Deep venous thrombosis (DVT) and associated pulmonary embolism (PE) are life-threatening complications following major orthopedic surgeries. Prevention of these complications remains challenging, and there is an increased interest in developing new drugs and treatment modalities. This is because DVT occurs in approximately

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Submitted: June 19, 2014 **Accepted:** September 02, 2014

Available online at
www.aott.org.tr
doi: 10.3944/AOTT.2015.14.0219
QR (Quick Response) Code

10% cases after total knee and hip replacement surgeries, despite routine prophylaxis regimens with low-molecular-weight heparin (LMWH) for 10 days after total knee replacement and 30 days after total hip replacement.[1,2]

LMWHs have been widely used for DVT prophylaxis after major orthopedic surgeries as part of the various guidelines for the prevention of venous thromboembolism (VTE).[3] The need for subcutaneous injections is a major issue that makes LMWH treatment complicated in the outpatient setting. New oral anticoagulants (NOAs) developed lately are now widely available and are suitable as LMWH replacements. These drugs have stable and predictive pharmacokinetic and pharmacodynamic profiles. Several studies have compared the efficacy and safety of enoxaparin and those of the direct thrombin inhibitor dabigatran and factor Xa inhibitor rivaroxaban for preventing DVT after hip and knee replacements.[4–11] In a meta-analysis of 16 studies with 38,747 patients, when compared with enoxaparin, the risk of symptomatic VTE was reported to be lower with rivaroxaban and similar with dabigatran and apixaban. In addition, compared with enoxaparin, the relative risk of clinically relevant bleeding was higher with rivaroxaban, similar with dabigatran, and lower with apixaban.[12] On the basis of these reports, the latest guidelines recommend NOAs for antithrombotic prophylaxis after total hip arthroplasty (THA) and total knee arthroplasty (TKA); however, LMWH is still the preferred agent over NOAs.[3]

In the current study, LMWH and NOA treatment modalities were combined to take advantage of the benefits of both modalities. LMWH was used during the hospital stay because of its proven safety profile, and NOAs were used during the outpatient period because of their ease of use. In the present study, we compared the safety and efficacy of 2 switch-therapy modalities—enoxaparin during the hospital stay and subsequent rivaroxaban during the outpatient period; enoxaparin during the hospital stay and subsequent dabigatran during the outpatient period—with enoxaparin monotherapy.

Patients and methods

In this prospective, non-blinded, randomized controlled study, 180 patients out of 247 patients undergoing TKA or THA and who met the inclusion criteria were randomized to receive either the standard treatment (2×0.3-mL enoxaparin during the hospital stay and 1×0.4-mL enoxaparin during the outpatient period for a total of 10 days after TKA and 30 days after THA; enoxaparin group), switch therapy with rivaroxaban (2×0.3-mL enoxaparin during the hospital stay and 1×10 mg rivaroxaban during the outpatient period for a total of 10 days after TKA and 30 days after THA; rivaroxaban group) and switch therapy with dabigatran (2×0.3-mL enoxaparin during the hospital stay and 1×220 mg dabigatran during the outpatient period for a total of 10 days after TKA and 30 days after THA; dabigatran group). While planning the study, we aimed to have 3 groups with 60 patients each. Between March 2011 and July 2013, a total of 247 THA and TKA operations were performed, and 180 patients who met the inclusion criteria were included in the study. The first 60 patients were assigned to the enoxaparin group, the second 60 patients were assigned to the rivaroxaban group, and the third 60 patients were assigned to the dabigatran group. Patients in the enoxaparin group (mean age, 67 years; range, 40–87 years; 22 males, 38 females; 30 TKA, 30 THA) were selected from a total of 81 possible patients, those in the rivaroxaban group (mean age, 65 years; range, 45–80 years; 17 males, 43 females; 28 TKA, 32 THA) were selected from a total of 79 possible patients, and those in the dabigatran group (mean age, 68 years; range, 49–82 years; 23 males, 37 females; 33 TKA; 27 THA) were selected from a total of 87 possible patients (33 TKA, 27 THA) (Table 1). Written informed consent was obtained from all patients.

Patients who had undergone TKA or THA with body weight >50 kg and age ≥18 years were included in the study. Exclusion criteria were as follows: those with an inherited or acquired clinically significant bleeding disorder; major surgery, uncontrolled hypertension, or myocardial infarction within the last 3 months; history of hemorrhagic stroke; gastrointestinal or urogenital bleeding within the last 6 months; severe liver disease; severe renal insufficiency (creatinine clearance <30 mL/min); active malignant disease; and platelet count $<100\times10^9$/L.

All patients were operated on by the same surgeon and pneumatic tourniquets were used during the TKA op-

Table 1. Study groups.

	Enoxaparin group	Rivaroxaban group	Dabigatran group
Mean age	67 (range, 40–87) years	65 (range, 45–80) years	68 (range, 49–82) years
Sex	22 male, 38 female	17 male, 43 female	23 male, 37 female
Total knee arthroplasty	30	28	33
Total hip arthroplasty	30	32	27

Table 2. Major and minor bleeding criteria.

Major and minor bleeding criteria
Major Bleeding
Fatal Bleeding
Bleeding causing a fall of >2 g/mL in hemoglobin or bleeding leading to transfusion of 2 U packed cells or whole blood
Bleeding requiring treatment cessation and/or operation
Symptomatic retroperitoneal, intracranial, intraocular, or intraspinal bleeding
Minor Bleeding
Skin hematoma of >25 cm^2
Wound hematoma >100 cm^2
Spontaneous nose or gingival bleeding lasting >5 min
Spontaneous rectal bleeding creating more than a spot
Spontaneous macroscopic hematuria or hematuria lasting >24 h in the presence of an urinary catheter

Table 3. Bleeding events.

	Enoxaparin group	Rivaroxaban group	Dabigatran group
Major bleeding during hospitalization	1	–	1
Minor bleeding during hospitalization	3	2	2
Minor bleeding during the outpatient period	2	3	2

erations. All the THA operations were performed under general anesthesia; however, only 20 of the 91 TKA operations were performed under general anesthesia (5 out of 30 in the enoxaparin group, 8 out of 28 in the rivaroxaban group, and 7 out of 33 in the dabigatran group). A 2×0.3-mL subcutaneous enoxaparin regimen was initiated 12 h after the surgery, and all patients received this regimen during the hospitalization period. Mean hospitalization times were 4.1, 4.2, and 4.1 days for the enoxaparin, rivaroxaban, and dabigatran groups, respectively. One dose of enoxaparin was skipped because of catheter removal during the 2nd or 3rd day after the operation for patients who had regional anesthesia. Patients in the enoxaparin group received 1×0.4-mL subcutaneous enoxaparin, patients in the rivaroxaban group received 1×10-mg rivaroxaban, and patients in the dabigatran group received 1×220-mg dabigatran during the outpatient period. Patients who had undergone TKA had a total of 10 days of DVT prophylaxis and patients who had undergone THA had a total of 30 days of prophylaxis.

The primary efficacy outcome was preventing symptomatic or Doppler ultrasonography (USG)-proven DVT or associated PE for 6 weeks after surgery. All patients were evaluated for DVT with Doppler USG at 6 weeks after surgery by the same radiologist. The cost of Doppler USG was undertaken by the institution. The primary safety outcome was incidence of bleeding during the DVT-prophylaxis period. Bleeding events were defined as major or minor according to previous studies.[6] Fatal bleeding; bleeding causing a fall of >2 g/mL in hemoglobin; bleeding leading to transfusion of 2 U packed cells or whole blood; bleeding requiring treatment cessation and/or operation; and symptomatic retroperitoneal, intracranial, intraocular, or intraspinal bleeding were considered major bleeding (Table 2). Ecchymosis >25 cm^2, wound hematoma, spontaneous nose or gingival bleeding lasting >5 min, spontaneous rectal bleeding creating more than a spot, spontaneous macroscopic hematuria, or hematuria lasting >24 h in the presence of an urinary catheter were considered minor bleeding (Table 2). Minor and major bleeding events were subclassified as during the hospitalization period and during the outpatient period for better understanding of the relative risk of bleeding associated with NOAs. Total number of bleeding events and bleeding events during the outpatient period were compared separately.

"SPSS for Windows" software was used for statistical analysis (NCSS Statistical Software, Kaysville, UT, USA). The safety and efficacy outcomes were compared by using a 1-way analysis of variance (ANOVA).

Results

Demographic and surgical characteristics of the 3 groups were similar. No DVT or PE events were observed during the postoperative 6-week follow-up period in the 180 patients. Doppler USG at 6 weeks after surgery did

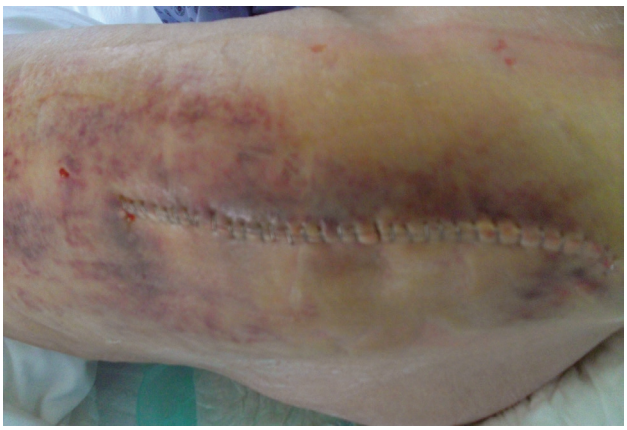

Fig. 1. A minor bleeding event after total hip arthroplasty. Wound hematoma >100 cm^2. [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

not reveal signs of DVT in any patients.

During the hospitalization period, only 2 major bleeding events were reported (1 [1.6%] in the enoxaparin group and 1 [1.6%] in the dabigatran group). No major bleeding events were reported during the outpatient period in any group. Five (8%) minor bleeding (Figure 1, Table 3) events were reported in the enoxaparin group (3 during the hospitalization period and 2 during the outpatient period), 5 (8%) minor bleeding events were reported in the rivaroxaban group (2 during the hospitalization period and 3 during the outpatient period), and 4 (6%) minor bleeding events were reported in the dabigatran group (2 during the hospitalization period and 2 during the outpatient period). There were no statistically significant differences in the total number of minor bleeding events and outpatient bleeding events among the 3 groups ($p>0.05$).

Discussion

The results of the current study showed that switch-therapy DVT-prophylaxis regimens, with enoxaparin during the hospitalization period and rivaroxaban or dabigatran during the outpatient period, are as safe and efficient as the enoxaparin monotherapy for DVT prophylaxis after THA and TKA. There was no statistically significant difference between complication rates and thrombosis-related events among the 3 groups; however, the number of patients in the study is not sufficient to extrapolate our results to the general population.

Although NOAs are newly developed alternatives to classic enoxaparin prophylaxis, the proven safety and efficacy profile of enoxaparin makes it the first-choice prophylaxis agent after major orthopedic surgeries.[3] There are many phase-III randomized clinical trials comparing NOAs with North American (2×0.3 mL) and European (1×0.4 mL) enoxaparin regimens. In the present study, the North American enoxaparin regimen was used during the hospitalization period, whereas the European enoxaparin regimen during the outpatient period.

Recently published meta-analyses of these phase-III trials shows similar results with minor differences. A pool analysis of 10 randomized controlled studies including 32,144 patients showed that NOAs are more efficient than the European enoxaparin regimen after THA and TKA, because they decrease the incidence of DVT and associated mortality with similar bleeding rates; however, the DVT incidence rates after NOAs are similar to those with the North American enoxaparin regimen.[13] In the current study, rivaroxaban was found to be the most efficient NOA for DVT risk reduction but had the highest incidence of bleeding events. Similar results were reported in another indirect comparison, which included 16 trials with 38,747 patients.[14] The previous study concluded that the higher efficacy of NOAs is generally associated with a higher bleeding tendency in patients undergoing TKA and THA. When compared with enoxaparin, the risk of symptomatic VTE was reported to be lower with rivaroxaban and similar with dabigatran and apixaban. In addition, when compared with enoxaparin, the relative risk of clinically relevant bleeding was reported to be higher with rivaroxaban, similar with dabigatran, and lower with apixaban. Another indirect comparison study between dabigatran and rivaroxaban reported that after THA and TKA, 10-mg rivaroxaban once daily decreases DVT risk relative compared with 220-mg dabigatran once daily, with no significant difference in the rates of major bleeding.[12] However, there are recent studies that favor rivaroxaban because of its better DVT-prophylaxis profile and similar safety outcomes. Lazo-Langner et al., after a study including 24,321 patients who had undergone a TKA or THA, reported that rivaroxaban was associated with a lower 30-day risk of hospitalization due to VTE than LMWH, with no significant difference in hospitalizations for major bleeding.[15] Levithan et al., in a risk–benefit assessment study, reported that rivaroxaban therapy after a THA or TKA, compared with enoxaparin therapy, resulted in more benefits and less adverse events, with benefits exceeding adverse effects, starting immediately after initiation of therapy through long-term follow-up.[16]

As stated above, the efficacy of NOAs is clearly proven with phase-III randomized controlled studies, but an increased risk of bleeding is also reported, especially with rivaroxaban. Major VTE events (proximal DVT as well as fatal and non-fatal PE) were reported to be 1.3% with NOAs and 2.2% with enoxaparin (American and Eu-

ropean regimens combined).[13] No major VTE events were observed in the current study. Major bleeding events were reported to be 0.8% with NOAs (with a slightly greater incidence with rivaroxaban) (relative risk, 1.88)) and 0.8% with enoxaparin (American and European regimens combined).[13] In the present study, 2 (1.1%) major bleeding events were observed during the hospitalization period, which is similar to previous studies; however, no major bleeding event was observed during the outpatient period.[17] In the current study, we did not see an increase in bleeding rates in the switch-therapy groups. The cause of the difference with previous studies may be because enoxaparin was used during the hospitalization period, when most of the major and minor bleeding events associated with surgery itself occur.

The main weakness of the current study was the small sample size. Future studies are needed with homogenized larger sample sizes to better understand the reliability of the current kind of switch-therapy modality. NOAs are new alternatives to enoxaparin for DVT prophylaxis after THA and TKA and have a proven safety profile, but their associated bleeding tendency makes enoxaparin first-choice prophylaxis choice. When using switch-therapy modalities, clinicians can take advantage of the safety of enoxaparin during the hospitalization period and ease of use of NOAs during the outpatient period, with a similar efficacy as enoxaparin monotherapy.

Conflics of Interest: No conflicts declared.

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