

Dabigatran versus Enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: A randomized clinical trial

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Original Article

Abstract

BACKGROUND: Venous thromboembolism (VTE) and deep vein thrombophlebitis (DVT) is a serious problem with high mortality and morbidity rates. This study was conducted to compare efficacy and safety results of the two types of VTE preventing in patients underwent total knee arthroplasty (TKA).

METHODS: Having considered exclusion criteria, 90 patients of 136 ones were registered in the study. Our patients of TKA were split randomly in two groups. Totally, 45 patients received enoxaparin, 40 mg 12 h before surgery and treated by 40 mg daily up to 15 days. The second group (45 patients) were treated by dabigatran 150 mg 4 h after surgery and 225 mg daily up to 15 days. Efficacy was evaluated by Doppler sonography after 15 days for the presence of DVT and safety was determined by 3 months follow-up for all-cause mortality and any major or minor bleedings.

RESULTS: Two groups were similar in baseline characteristics. The efficacy outcome events occurred in 2.2% (2 of 90) of the patients (1 symptomatic VTE in dabigatran and 1 in the enoxaparin group) without significant statistical difference between groups ($P = 0.64$). In terms of safety, 3 patients (6.6%) in dabigatran and 2 patients (4.4%) in enoxaparin group had major bleeding ($P = 0.66$) and 8 patients (17.7%) in dabigatran and 7 patients (15.7%) in enoxaparin group had non-major bleeding event ($P = 0.81$). There were no death, pulmonary emboli, and cardiac events during follow-up.

CONCLUSION: Three months follow-up did not show statistical difference in efficacy and safety between dabigatran and enoxaparin. Future studies with mentioning to later outcomes for checking safety are warranted.

Keywords: Dabigatran, Prevention, Venous Thromboembolism, Enoxaparin, Total Knee Replacement

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Introduction

Venous thromboembolism (VTE) is serious disease with high rate of mortality and morbidities¹ which lead the scientist to recommend some guideline for prevention.² However, recently, new agent oral drugs have been introduced which make the long-term VTE prophylaxis more comfortable.³ One of these drugs is dabigatran, which is a thrombin inhibitor and can be initiated post operatively.⁴ This is an important advantage because on a practical

level, the exact time for operation is uncertain and affected by preparation time, delays from previous surgical cases. Hence, in contrast to dabigatran, which administered post operatively, using enoxaparin preoperatively may be difficult to ensure that the dose given provides adequate coverage during the operation.⁵ Therefore, nowadays using of oral preventive drugs is increasing.

VTE as a pulmonary embolism (PE) is a serious problem with high mortality and morbidity rates.^{6,7}

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Major orthopedic surgeries like total knee arthroplasty (TKA) with inducing endothelial damage, reducing venous return and subsequent blood stasis, are responsible for 50% of thromboembolic events in the absence of venous thromboembolic prophylaxis. High incidence of VTE, is leading to recommend evidence-based guidelines in preventing VTE after major orthopedic surgeries.⁸⁻¹⁰

In many European countries, low-molecular-weight heparin (LMWH) is used as standard therapy for prophylaxis of VTE and initiates preoperatively. However, the limitations include parenteral administration, an indirect mode of action, inability to inhibit clot-bound thrombin and association with complications such as heparin-induced thrombocytopenia are discussed for this prophylactic method. Therefore, the introduction of new oral agents like dabigatran etetexilate may alleviate guideline adherence in terms of oral medication instead of injection routes and without the need for routine coagulation monitoring.

Dabigatran etetexilate is a thrombin inhibitor which its plasma concentration is not substantially altered by age, gender or body weight, and fixed dose of dabigatran etetexilate can be used in most patients.^{11,12} With the necessity of prolong prophylaxis in patients underwent major orthopedic surgeries; using oral agent with no need to monitoring is seemed rational compared with parenteral agents. However, the safety and efficacy of dabigatran compared with traditional drugs like LMWH is also important. Hence, this study conducted to compare efficacy and safety results of the two types of VTE preventing in patients underwent TKA.

Materials and Methods

This prospective randomized trial was conducted from November 2011 to June 2012 in the Department of Orthopedic Surgery at Shariati Hospital (Medical school of Islamic Azad University, Najafabad branch) in Isfahan, Iran. Patients with expected primary TKA, more than 18-year-old participated in the study. Exclusion criteria were any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the

normal range within the past month; severe renal insufficiency (creatinine clearance < 30 ml/min); using non-steroidal anti-inflammatory drugs (NSAID) within a week before surgery; active malignant disease. The study was approved by the Ethics Committee of Azad Islami University of Najafabad Branch, and each patient gave informed consent prior to the study, which was performed in accordance with the ethical standards of the 1964 declaration of Helsinki as revised in 2000 with IRCT number 2013082513828N2.

Allocation: After registering demographic data, laboratory exams containing cell blood counts were performed by cell counter Sysmex KX 21 and prothrombin time (PT), partial thromboplastin time (PTT), blood urea nitrogen, creatinine, ALT and aspartate amino-transferase were performed by Hitachi 902. Of the 136 patients initially enrolled in the study, 46 were not included in the final analysis. Of the 46 patients who did not meet the inclusion criteria, 12 patients had history of stroke or myocardial infarction, 20 patients used NSAID within a week prior to TKA, and eight patients had uncontrolled hypertension within prior 3 months. Six patients were unable to get the anesthesiologist's permission for the operation. Remaining 90 patients were randomized based on a table of random numbers generated by random allocation software in regard to simple random allocation¹² by the principal investigator into two groups (LMWH and dabigatran) and underwent TKA in order to technique previously described.¹³ In first group (n = 45) enoxaparin (40 mg) 12 h before surgery were used and continued daily to 15 days and in second group (n = 45) dabigatran etetexilate - manufactured by boehringer ingelheim 150 mg were started 4 h after surgery and continued with 225 mg daily to 15 days. All patients were followed for 3 months. The treatment period was defined as the time from the first dose to 3 days after the last oral or subcutaneous dose, whichever came later.

Symptomatic and asymptomatic deep vein thrombophlebitis (DVT) and/or symptomatic PE and all-cause mortality, during treatment, were our primary efficacy outcomes. Bilateral Doppler sonography was performed by GE S6 machine at 15 days after first dose treatment for prevention of DVT. PE was diagnosed by ventilation/perfusion scintigraphy, spiral computed tomography. Radiologist who was blinded to trial also applied diagnostic tests for DVT events.

Occurrence of bleeding event during treatment was our primary safety outcome. We considered major bleeding events¹⁰ as: Clinically overt bleeding

associated with ≥ 20 g/l fall in hemoglobin; clinically overt bleeding leading to a transfusion of ≥ 2 units of packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding and bleeding warranting treatment cessation or leading to reoperation.

Non-major, clinically relevant on treatment including spontaneous hematoma ≥ 25 cm³, wound hematoma ≥ 100 cm³, epistaxis > 5 min, spontaneous hematuria or a prolonged one after intervention, spontaneous rectal bleeding, gingival bleeding > 5 min were our secondary safety outcomes.

Laboratory tests were performed on the last day of dosing, at 4-6 weeks and 3 months after surgery. All cases of hepatic enzyme abnormalities and suspected cardiovascular events during the study were discontinued the drug and referred to related specialist.

Considering $\alpha = 0.05$, study power = 80%, $d = 0.15$ points as the minimal expected difference between the two groups with $P1$ and $P2 = 0.07$ (the probably incidence of thromboembolism in TKA), a sample size of 45 patients was considered for each group. SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) was used to analyze the data using the independent T-test and the fisher exact test for comparing means and percent for quantitative and qualitative data, respectively, between the two groups. $P < 0.05$ were considered as statistically significant.

Results

A total of 136 patients was considered for the study,

but 46 patients were excluded due to past medical history or medications that interfere that our study and finally 90 patients with written consent was enrolled. 38 male (42%) and 52 female (58%). The mean age of our patients was 70 ± 9 . The flow of participants is shown in the CONSORT diagram in figure 1. The mean time interval between TKA and performing of Dabigatran was 4 h and the median oral treatment duration was 7 days. The pre-operative, baseline characteristics of the two groups are shown in table 1.

The efficacy outcome including symptomatic VTE and/or symptomatic PE and all-cause mortality occurred in 2.2% (2 of 90) of patients. The incidence of the primary outcome is shown in table 2. According to fisher test, there is no significant difference between enoxaparin group versus dabigatran group.

The safety outcome was shown in table 3. Five patients developed major bleeding during treatment. There is no statistical difference between Dabigatran and Enoxaparin in safety primary and secondary outcomes ($P = 0.66$, $P = 0.81$).

Significant liver enzyme elevation (ALT levels more than 3 times of upper limited of normal) was reported in 2.2 and 4.4% of dibigatran and enoxaparin groups. Hence, the two groups were similar in terms of liver function abnormality ($P = 0.56$). In all cases, the abnormalities returned to the baseline measurement with additional follow-up. Acute coronary events were not occurred in any patients during follow-up.

Table 1. Baseline characteristics of patients

Characteristics	Dabigatran (n = 45)	Enoxaparin (n = 45)	P
Age*	72.1 \pm 9.3	68.3 \pm 10.1	0.72**
Weight*	77.3 \pm 7.6	80.6 \pm 10.1	0.85**
Sex (Female) (%)*	28 (62.2)	30 (66.6)	0.97***

* Data are presented as number, mean, standard deviation and percent; ** Independent t test; *** Chi-square test

Table 2. Efficacy outcomes during treatment period

Characteristic	Dabigatran (n = 45)	Enoxaparin (n = 45)	P**
Symptomatic DVT (%)*	1 (2.2)	1 (2.2)	0.99
Symptomatic PE*	0	0	0.99
Death*	0	0	0.99

* Data are presented as number and percent; ** Fisher exact test; DVT: Deep vein thrombophlebitis; PE: Pulmonary embolism

Table 3. Safety outcomes during treatment period

Characteristics	Dabigatran (n = 45) (%)	Enoxaparin (n = 45) (%)	P**
Major bleeding*	3 (6.6)	2 (4.4)	0.66
Non-major bleeding*	8 (17.7)	7 (15.5)	0.81
Elevated of liver enzyme*	1(2.2)	2(4.4)	0.56

* Data are presented as number and percent; ** Chi-square test

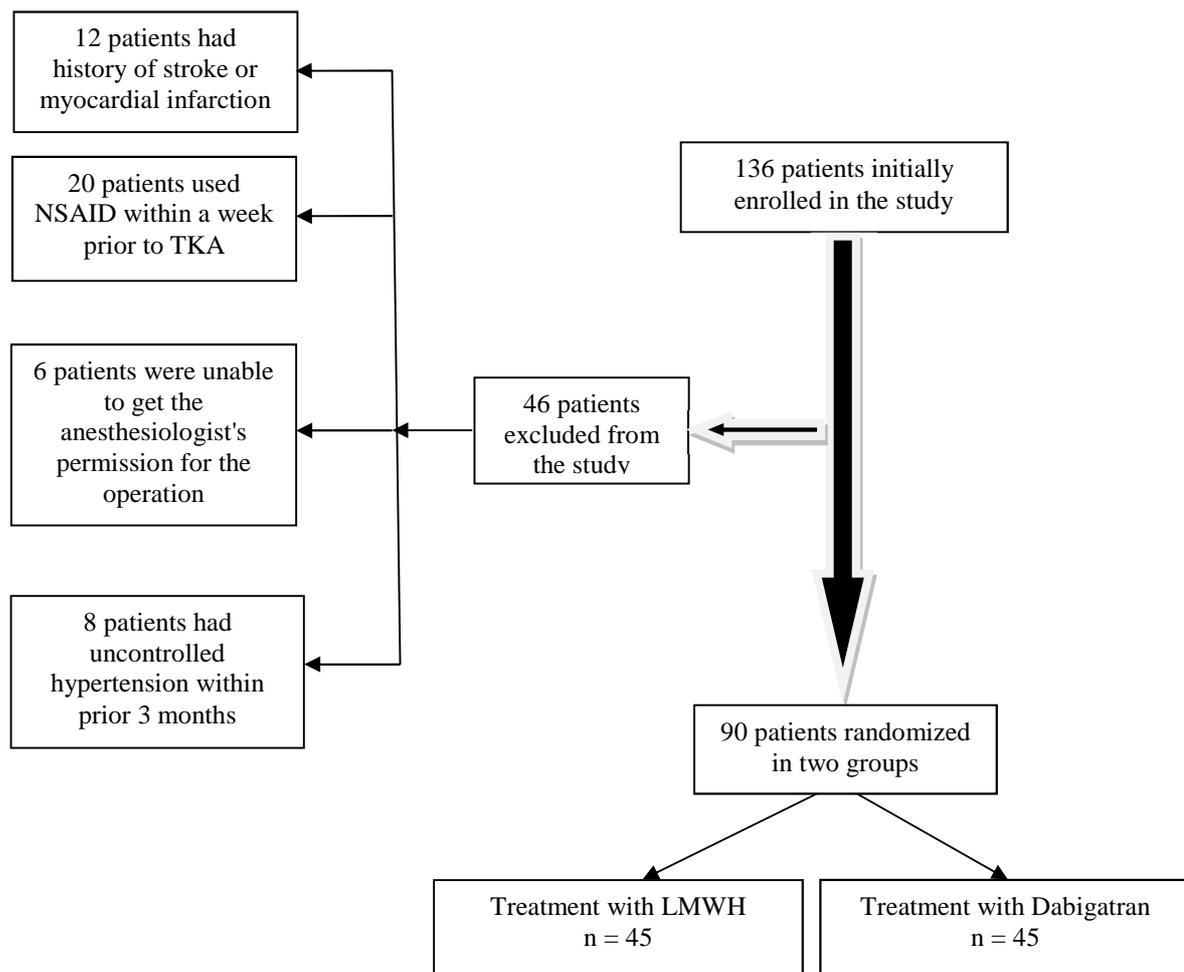


Figure 1. Trail chart of study participants
NSAID: Non-steroidal anti-inflammatory drugs; TKA: Total knee arthroplasty;
LMWH: Low-molecular-weight heparin

Discussion

The most important finding of this study was no difference between dabigatran and enoxaparin in the prevention of VTE after TKA. Furthermore, this study showed a good efficacy and safety for dabigatran that was comparable with enoxaparin.

We showed that no significant difference between dabigatran and enoxaparin in efficacy and safety outcomes. Our finding supported previous studies.^{12,13} Three major trials have been designed in comparison of dabigatran and enoxaparin in safety and efficacy. The RE-NOVATE II trial¹² compared dabigatran etexilate, 220 mg (n = 1157) or 150 mg (n = 1174) once daily with subcutaneous enoxaparin, 40 mg (n = 1162) once daily in patients underwent hip replacement. The RE-MODEL¹³ also compared dabigatran etexilate, 220 mg (n = 694) or 150 mg (n = 708) once a day with subcutaneous enoxaparin, 40 mg (n = 699) once

daily in patients underwent TKA. In both above studies, dabigatran has comparable results compared with enoxaparin in the primary efficacy outcomes^{12,13} which supported our results.

In RE-MODEL trial,¹³ 37.7% and 36.4% of primary efficacy outcomes were occurred in enoxaparin and dabigatran (220-mg group) groups. Our findings showed 2.2% of patients in Dabigatran and enoxaparin groups experienced efficacy outcomes events. Although the rates of the primary efficacy outcome were higher in the RE-MODEL trial, but there were no significant differences between groups. Also, this difference may be due to lower sample size in our study.

In terms of safety, both mentioned trials showed same major bleeding rates in dabigatran versus enoxaparin group.^{12,13} In RE-NOVATE II, major bleeding was shown in 1.6% of the enoxaparin group, compared with 2.0% of the dabigatran

etexilate 220 mg group.¹² In RE-MODEL, major bleeding events demonstrated in 1.3% of the enoxaparin group, compared with 1.5% of the dabigatran etexilate 220 mg group.¹³ Our study showed 4.4% of patients in the enoxaparin group and 6.6% of patients in the dabigatran group had major bleeding event. This is similar between our study and these two trials, which no significant difference has been found between two groups.

In contrast of our findings, RE-MOBILIZE trial¹⁴ which compared 30 mg enoxaparin twice daily with dabigatran etexilate, 220 mg or 150 mg once daily showed numerically fewer major bleeding events in the dabigatran group. It may be because of higher dose of enoxaparin compared with our study.

Our study showed no statistical difference in term of between liver enzyme elevations, bleeding outcomes and incidence of acute coronary events between dabigatran and enoxaparin. Furthermore, these findings are supported with above three trials findings.

Our study has strengths including double blinding randomization design and enough follow-up without losing any patient. A limitation of our work is low sample size.

Conclusion

Three months follow-up did not show statistical difference in efficacy and safety between dabigatran and enoxaparin. Also with high prevalence of DVT after major surgery in Iran, Future longer studies with longer follow-up recommended to check the exact effect of dabigatran in preventing DVT.

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Conflict of Interests

Authors have no conflict of interests.

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