

Thromboprophylaxis in Patients undergoing Orthopedic Surgeries; Focus on cost-effective analysis and safety comparison between Rivaroxaban and Enoxaparin.

Protocol study

*Submitted for partial fulfillment of Doctorate of Philosophy in Clinical pharmacy by: **Ahmed A H Ali***

MSc, BCPS, BCACP

Under supervision of:

Prof. Hesham Boshra Al Said Mahmoud

Professor of Cardiology, Faculty of Medicine, Beni-Suef University.

Dr. Ahmed Abdullah Hassan Elberry

Associate Professor of Clinical Pharmacology, Faculty of Medicine, Beni-Suef University.

Dr. Emad Gaber Kamel Elbana

Associate Professor of orthopedic surgery, Faculty of Medicine, Beni-Suef University.

Dr. Raghda Roshdy Sayed Hussein

Lecturer of Clinical Pharmacy, Faculty of Pharmacy, Beni-Suef University.

Introduction

In general, many surgeries put patients at a great risk for venous thromboembolism (VTE) and potential fatal consequences, including pulmonary embolism. Despite significant advances in the pharmacotherapy of prevention and treatment of VTE, pulmonary embolism still remains a common preventable cause of death in hospitals. Therefore, efforts vitally should be continued to pursue advances toward the safest and most effective means of preventing and managing VTE.

There is a Today consensus that patients undergoing high-risk surgery should receive prophylaxis against postoperative venous thromboembolism (VTE). A good example of that could be orthopedic surgeries which place patients at unnecessary increased risk of fatal pulmonary embolism. For many years, pharmacotherapy options have been recommended by the American College of Chest Physicians (ACCP) for postoperative thromboprophylaxis were low-molecular-weight heparins (LMWHs), fondaparinux, and warfarin. However, their limitations have been repeatedly demonstrated in a huge number of randomized controlled trials (RCTs).

[1,2]

Since its introduction, low-molecular-weight heparins (LMWHs) are still common used in practice as thromboprophylactic agent. But, they require subcutaneous administration which making it challenging for use in settings other than the inpatient one. Despite the lower incidence of low-molecular-weight heparins (LMWHs) induced heparin-induced thrombocytopenia (HIT) compared with unfractionated heparins (UFH) in the postoperative setting, the risk of LMWH induced HIT in patients treated for VTE still concerns many clinicians. In addition to its subcutaneous administration, fondaparinux is contraindicated in severe renal impairment patients (with creatinine clearance (CrCl) <30 milliliter/minute) and those who have low body weight (<50 kg; VTE prophylaxis only). While available orally, Vitamin K antagonists (VKAs) like Warfarin have unpredictable pharmacologic effects requiring a wakeful monitoring. Warfarin is also a remarkable source of food and drug interactions. As a result, it is mandatory to search for novel drugs or at least to search for new indications of really existing drugs. [2]

In July 2011, the Food and Drug Administration (FDA) approved an orally administered selective factor Xa inhibitor called Rivaroxaban for the prevention of deep vein thrombosis (DVT) after total hip replacement (THR) or total knee

replacement (TKR) surgeries. According to the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism (RECORD) trials, rivaroxaban demonstrated superiority to enoxaparin in reducing venous thromboembolism without significant increase of bleeding risk. Rivaroxaban is recommended to be used at a fixed dose of 10 mg daily, with or without food, for 35 days following THR or 12 days following TKR. [3]

Although the US Food and Drug Administration (FDA) advisory committee has recommended approval of rivaroxaban, many questions have been raised on the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism (RECORD) trials of rivaroxaban. Some may argue that dosing was inconsistent with the recommendations. Others went far to say that the duration of treatment was inconsistent and did vary with enoxaparin. In other words, it was somewhat short.

Results from the ORTHO-TEP registry on joint replacement arthroplasty (hip and knee) from Dresden, Germany and Xarelto® in the Prophylaxis of Postsurgical Venous Thromboembolism after Elective Major Orthopaedic Surgery of the Hip or Knee (XAMOS) study are in accordance with the conclusion of Regulation of Coagulation in Major Orthopedic surgery reducing the Risk of DVT and PE (RECORD) trials. A subset of countries that participated in XAMOS also included patients undergoing fracture-related orthopedic surgery. [1,3,4]

Surgery as a therapy for cancer may double the risk of venous thromboembolism. However, results from studies including SAVE-ONCO, PROTECHT, and FRAGEM have been used as a backbone of recommendation for VTE prophylaxis in cancer patient, no controlled one has compared the new anticoagulant like Rivaroxaban with the standard of care therapy drugs [6]. All these new drugs including rivaroxaban have not been intensively studied in patients undergoing day-surgery. High risk VTE ambulatory surgical patients such as patients with a previous episode of VTE or with additive risk factors may benefit from rivaroxaban. [7].

It is a hot topic of debate to accept standard method of VTE prevention in plastic surgery. In a retrospective experience of 2 surgical centers that use rivaroxaban for routine VTE prophylaxis for patients undergoing abdominoplasty, Oral rivaroxaban administration for chemoprophylaxis in abdominoplasty patients is safe, with low

rates of symptomatic VTE and hematoma formation. The authors recommended routine use of the medication for patients at increased risk for VTE events. Regarding other trials that compare rivaroxaban by standard of care drugs, we can't find direct comparison between the two regimens. [8]

Similarly, no controlled trials have evaluated the role of rivaroxaban as a new oral anticoagulant in Venous thromboembolism (VTE) prophylaxis for other nonorthopedic surgical patients. According to American College of Chest Physicians (ACCP), 2012 recommendation for thromboprophylaxis for general, abdominal-pelvic surgery, thoracic, cardiac surgery and Gynecological surgery, it is recommended to weigh the risk of thrombosis against the bleeding risk before adding LMWH or unfractionated heparin.

Moreover, very few randomized clinical trials (RCTs) are powered to study side effects when comparing substances, and even large RCTs may be too small to reveal rare side effects. It seems difficult to compare safety data from trial to trial because there is no standardized definition of bleeding. One prospective study collecting data from the electronic health record at two institutions concluded that using of enoxaparin for VTE prophylaxis following THA and TKA was associated with a lower rate of the primary outcome (any postoperative bleeding) compared with the use of rivaroxaban in a similar cohort of patients. However, it was a retrospective investigation with many limitations can be argued with regard to selection and change in practice guideline during the study period.

Finally, there is lack of literature data that define rivaroxaban as orthopedic postoperative thromboprophylactic agent rather than well-known indications (hip and knee replacements). It also is not plausible to accurately compare safety data with other injectable anticoagulants.

Aim of the work

The main objective is to reduce the incidence of venous thromboembolism (VTE) in orthopedic postoperative patients based on the potential benefit of using rivaroxaban as a monotherapy.

It is around efficacy and safety evaluation of using rivaroxaban as a monotherapy prophylactic agent in patients undergoing orthopedic surgeries taking into the account the reliable selection of patients most benefit.

Answering questions about additional cost benefit from the perspective of the cost-effective analysis on extrapolating the results emerged to our university teaching hospital setting are going to be evaluating as well.

Methodology

Study design and randomization

It is proposed to randomly assign at least 100 patients sequentially based on admission; in a single blind, interventional trial, to two separate groups. Patients are going to be selected from our university teaching hospital. patients were randomly assigned to a study group with the use of permuted blocks and stratification using well trusted randomization websites or software programs (SAS). Permuted block randomization list will be transferred from alphabetic symbol by the competent orthopedic supervisor and coded based on the randomization order by manual coding preset by orthopedic supervisor [5]. Double dummy technique may be feasible here as long as we tackled difficulty of providing syringes containing saline. However, the risk of injecting a saline solution subcutaneously (i.e. bleeding complications may develop in persons taking an anticoagulant agent plus unnecessary injections) may outweigh the benefit. Since the investigator do not know which therapy is administrated, the potential for the results to be biased is minimized [6].

The first group is to be on rivaroxaban with dosage according to the orthopedic approved regimen (10 mg once daily 6-10 hours after the surgery; recommended total duration of therapy: 12 to 14 days; ACCP recommendation: Minimum of 10 to 14 days; extended duration of up to 35 days suggested (Guyatt 2012).[3]

The other group will be administered the standard of care (SOC) enoxaparin. Dosage and duration of therapy are illustrated in Table 1 [2].

Drug	Dosage and Duration
Enoxaparin	Once-daily dosing: 40 mg once daily, with initial dose within 9 to 15 hours before surgery, and daily for at least 10 days (or up to 35 days postoperatively) or until risk of DVT has diminished or the patient is adequately anticoagulated on warfarin. The American College of Chest Physicians recommends initiation ≥ 12 hours preoperatively or ≥ 12 hours postoperatively; extended duration of up to 35 days suggested (Guyatt, 2012).

Table 1: *Dosing of SOC drugs used in thromboprophylaxis after orthopedic surgery.*

It is expected here that all medication will be taken for a duration of 10 days after surgery. The type, duration and dose of the thromboprophylactic agents will be discussed with and determined by the competent physician before saying a particular patient can be enrolled.

Study population

The Patients >18 years who are going to be scheduled to undergo orthopedic surgery in whom decision of thromboprophylaxis taken will be enrolled for inclusion.

Exclusion criteria are based on the approved contraindication listed, for all drugs used, in the drug’s labels and supplemented by data from well trusted compendia like Lexi comp® or Micromedex®. The exclusion criteria are as follows, but not limited to:

- I. Severe hypersensitivity to drugs or any component of the formulation.
- II. Planned intermittent pneumatic compression
- III. A requirement for anticoagulant therapy that could not be stopped
- IV. Severe hypersensitivity reaction (eg, anaphylaxis) to rivaroxaban or enoxaparin.
- V. Received another anticoagulant for more than 24 hours
- VI. Active bleeding or a high risk of bleeding
- VII. Thrombocytopenia associated with a positive test for antiplatelet antibody.
- VIII. Warfarin associated INR more than 1.5 on the day of the surgery
- IX. Conditions preventing bilateral venography
- X. ICU stay after surgery
- XI. Pregnant or breast-feeding

- XII. Creatinine clearance less than 30 ml per minute or acute renal failure before the surgery or at any point during the study period.
- XIII. Moderate or Severe (Child Pugh B or C) hepatic Impairment or in patients with any hepatic disease associated with coagulopathy.
- XIV. Concomitant use of drugs that are both p-glycoprotein inhibitors and moderate to strong cyp3a4 (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir & conivaptan)
- XV. CrCl 15 to 80 mL/min PLUS both P-glycoprotein inhibitors and moderate CYP3A4 inhibitors (eg, abiraterone acetate, diltiazem, dronedarone, erythromycin, verapamil)

The study draft will be submitted to our ethics committee attached to the hospital administration board before enrollment of patients.

Prescribed co-medication of interest.

Because of the well documented effect of drugs affecting CYP3A4 co-prescribed with rivaroxaban, strong inhibitor and inducers listed on <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/> under the guidance of US Food and Drugs Administration(FDA) are contraindicate with rivaroxaban. Patient on these interacting drugs will be excluded.

Outcome measure and follow up.

The primary efficacy outcomes are the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or death up to 30 days. The main secondary efficacy outcome is major venous thromboembolism, which is defined as the composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death from venous thromboembolism.

The main safety outcome is the incidence of major bleeding beginning after the first dose of the study drug and up to 2 days after the last dose of the study drug (on-treatment period). Major bleeding is defined as bleeding that is fatal, occurs in a critical organ (e.g., retroperitoneal, intracranial, intraocular, and intraspinal bleeding), or requires reoperation or extra surgical-site bleeding that was clinically overt and is associated with a fall in the hemoglobin level of at least 2 g per deciliter or that requires transfusion of 2 or more units of whole blood or packed cells. Other safety outcomes include any on-treatment bleeding, any on-treatment non- major

bleeding, hemorrhagic wound complications (a composite of excessive wound hematoma and reported surgical-site bleeding), any bleeding that starts after the first oral dose of rivaroxaban and ended up to 2 days after the last dose is administered, adverse events, and death.

Validated clinical prediction rule is recommended to estimate pretest probability of venous thromboembolism. Duplex ultrasonography is the preferred test to diagnose DVT [7]. Many prediction scales are available like *Wells Clinical Models for Evaluating the Pretest Probability of VTE*.

Symptoms and signs of DVT may include unilateral leg swelling, pain in the affected leg, calf tenderness in affected leg, increased leg warmth, erythema of affected leg, or a “palpable cord” may be felt in the affected leg.

Regarding PE, diagnosis is suspected in patients with dyspnea, tachypnea, pleuritic chest pain, cough, and/or fever. Diagnosis begins with initial risk stratification based on presence of shock or persistent hypotension to identify patients at high risk of early mortality.

For patients with suspected high-risk PE with shock or hypotension, emergency computed tomography(CT) angiography beside transthoracic echocardiography is recommended depending availability and clinical circumstances. While for patients not suspected of having high-risk PE, clinical assessment of likelihood of PE using validated prediction rules and clinical judgement to distinguish between low and high-risk PE may use [8]. However, PE can be diagnosed based on computed tomography pulmonary angiography (CTPA). CT pulmonary angiography is preferred method when available.

It is recommended to have baseline Scr and platelets count. Based on Heparin induced thrombocytopenia, it is advisable to monitor platelets count beginning of the fourth day and every three days until discontinue of Heparins.

Data analysis

The patients in the two groups will be matched in advance for the difference in Patients’ characteristics, VTE risk factors, history of VTE, types of surgery, types of anesthesia and duration of surgery. This ensures fair randomization between groups. Statistical analysis will be performed at an overall significance level of 0.05, adjusted for the primary and secondary end points using non- independent t-test

(SPSS software). Comparisons of the primary end points between treatment groups were performed by means of a log-rank test. To estimate the size of the effect, we will use a Cox regression model. On the other hand, the cost-effective analysis (CEA) will be based mainly on estimating the average cost-effective ratio(ACER) and the incremental cost for each additional cure.

References

1. Beyer-Westendorf J, Lützner J, Donath L Et al. Efficacy and safety of thromboprophylaxis with low-molecular weight heparin or rivaroxaban in hip and knee replacement surgery. Findings from the ORTHO-TEP registry. *Thromb. Haemost.* 109(1), 154–163 (2013).
2. Guyatt GH, Akl EA, Crowther M, et al. Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012, 141(2 Suppl):7-47.
3. Lassen MR, Gent M, Kakkar AK, Eriksson BI, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. *J Bone Joint Surg Br.* 2012 Nov;94(11):1573–8.
4. Granero J, et al. Rivaroxaban versus standard of care in venous thromboembolism prevention following hip or knee arthroplasty in daily clinical practice (Spanish data from the international study XAMOS). *Rev Esp Cir Ortop Traumatol.* 2016 Jan-Feb;60(1)
5. Jimmy Efird. Blocked Randomization with Randomly Selected Block Sizes. *Int. J. Environ. Res. Public Health* 2011, 8(1), 15-20.
6. Kendrach M.G., Freeman M, Hughes P.J. (2013). Drug Literature Evaluation I: Controlled Clinical Trial Evaluation. In Malone P.M., Kier K.L., Stanovich J.E., Malone M.J. (Eds), *Drug Information: A Guide for Pharmacists 5e*. Retrieved November 06, 2016 from <http://accesspharmacy.mhmedical.com/content.aspx?bookid=981&Sectionid=544> 8066
7. Kearon C, Akl EA, Comerota AJ, et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 Feb;141(2 Suppl):e419S-94S.
8. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014 Nov 14;35(43). *Ann Intern Med.* 2015 Nov 3;163(9):701-11.



Dear Researcher: Pharmacist/ Ahmed A. Hassan Ali

Please be advised that (FM-BSU REC) has Reviewed on its meeting dated 22nd of January 2017 the protocol titled:

"Thromboprophylaxis in Patients undergoing Orthopedic Surgeries; Focus on cost-effective analysis and safety comparison between Rivaroxaban and Enoxaparin"

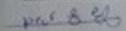
The FM-BSU REC has APPROVED the protocol from the Ethical point of view.

FMBSU REC is organized and operated according to Guidelines of the Declaration of Helsinki, International Conference of Harmonization ICH, and United States Codes of Federal Regulations and registered in under the Federal-wide Assurance (FWA) for the Protection of Human Subjects.

FWA #: FWA00015574
Expires: 04/25/2018

As a Principal Investigator You will need to:

- If Applicable, To Notify the Contact person of the FMBSU REC within 24 hours for any Serious Adverse Events (SAE) experienced by participants of the Study or as reported to you by the Sponsor / Manufacturer/ Co- Investigators in your site and within 5days for any other site locally and annually for any other site Internationally.
- If Applicable, To Suspend any new recruitment till you receive a response from FMBSU REC regarding these SAE.
- You may not initiate changes in approved research protocol without FMBSU REC Review and approval except when necessary to eliminate apparent immediate hazards to study subjects.
- This Approval is valid only for one Year starting from the 23rd of January 2017.


Prof. Dr. Ekram El Shabrawy
Chair of FMBSU REC
22/1/2017
Faculty Of Medicine
REC
Beni Suez University
Page 1 of 1


Walid Al-Shraby
Coordinator of FMBSU REC
22-Jan-2017