

Effectiveness of Alternating Thromboprophylaxis from Enoxaparin to Rivaroxaban after Total Knee Arthroplasty

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Abstract

Introduction: Rivaroxaban is demonstrated increasing the risk of major bleeding. The enoxaparin/rivaroxaban modified scheme may favorite the control of minor bleeding.

Materials and Methods: 156 patients were included after knee arthroplasty and they randomized in the group of switching thromboprophylaxis and the monotherapy group.

Results: One minor bleeding was observed in each study group during hospital stay. There was no statistically significant difference between complication rates and thrombosis-related events among the two groups.

Conclusions: The enoxaparin/rivaroxaban modified scheme with the benefits that offer, provides safe and effective anticoagulation prophylaxis after total knee arthroplasty.

Keywords: Total Knee Arthroplasty; Rivaroxaban; Enoxaparin; Tranexamic Acid

Introduction

Despite low-molecular-weight-heparin (LMWH) prevention, $\approx 0.5\%$ of patients when hip arthroplasty and $\approx 1\%$ when knee arthroplasty suffer symptomatic deep venous thromboembolism (DVT) before hospital discharge [1]. When considering death, symptomatic venous thrombosis, and major hemorrhage, rivaroxaban resulted in larger advantages compared with enoxaparin. Rivaroxaban additionally ends up in larger profit for total knee arthroplasty (TKA) and is balanced with enoxaparin for total hip arthroplasty (THA) [2]. Deep venous thromboembolism (DVT), pulmonary embolism (PE) and mortality occurred less oftentimes in patients taking rivaroxaban compared with enoxaparin (1.1% vs 3.7% when hip arthroplasty and 9.6% vs 18.9% when knee arthroplasty) [3,4]. Although rivaroxaban was a lot of useful than enoxaparin for preventing symptomatic DVT when a total joint operation was ascertained, associate degree enlarged risk of major hemorrhage and trauma wound complications [5-9]. Risk of relevant hemorrhage is higher with rivaroxaban than with enoxaparin and therefore, the same tendency exists also vs. dabigatran [10]. The effectiveness and safety of rivaroxaban in orthopedic surgery were maintained regardless of the temporal arrangement of the primary postoperative dose, the kind of anesthesia, and therefore the further

use of mechanical thromboprophylaxis [11]. Use of non-steroid anti-inflammatory drugs (NSAIDs) in XAMOS was related to a better frequency of hemorrhage events in patients receiving rivaroxaban [12]. We have a tendency to advise the changed thromboprophylaxis protocol of associate degree initial patient course with LMWH (s.c.) postoperatively, then switch to rivaroxaban (p.o.) upon hospital discharge. The purpose of our study is to evaluate the enoxaparin/rivaroxaban modified scheme of anticoagulation prophylaxis after total knee arthroplasty.

Materials and Methods

All consecutive 156 patients were included in our study after elective, primary knee arthroplasty between 15 April 2014 and 15 March 2017. All patients received a total knee arthroplasty by the same surgical team. Patients not fulfilling inclusion criteria were excluded from the study (previous operations of the knee, revision surgery, deformation of the mechanical axis of the knee ≥ 150 , instable-deficient ligament knee preoperative). Demographic data from study groups are present in table 1. Rivaroxaban was given mainly for VTE prophylaxis after knee replacement surgery for 25 days. In our study, the patients were randomized in two groups. At the first study group (75pt), option one was administered rivaroxaban 10 mg, once daily (OD) to start 6 - 10 hours postoperatively and to continue for 25 days after knee arthroplasty. At the second study group (81pt), option two was administered enoxaparin, 40 mg OD to start 6 - 12 hours postoperatively and to continue for the remainder of hospital admission. In the latter, enoxaparin is replaced by rivaroxaban, 10 mg OD upon hospital discharge to achieve a cumulative duration of anticoagulation of 25 days after knee arthroplasty.

	Group A (TRX-RIV)	Group B (TRX-LMWH/RIV)
Age	73.9 (range 69 - 82) years	71.7 (range 35 - 80) years
Sex	48 Female/27 Male	53 Female/28 Male
BMI	35	29.5
TKA	75	81
ASA	1.8	1.6
Mech.Ax.	7.0	7.3

Table 1: Study groups.

Abbreviations: TRX: Tranexate acid; RIV: Rivaroxiban; LMWH: Low molecular weight heparin; PLC: Placebo; TKA: Total knee arthroplasty, BMI: Body mass index, Mech.Ax: Mechanical axes deviation, ASA: American society anesthesiologists.

All the patients were treated with intraoperative administration of tranexamic acid, 10 mg/Kg iv and 1000 mg/20 ml tranexamic acid intraarticularly. One intra- articular drain was used with open drainage (i.e., without compression of the bag) during the first 48h after surgery. The drain remained closed for 2 hours postoperatively. The drains were removed on the second postoperative day (POD) no matter what the drain output was. All TKAs were unilateral and were cemented using the same prosthesis (EVOLUTION TM Medial pivot knee-Wright). An intramedullary alignment rod was used for femoral preparation and an extramedullary guide system for tibia preparation. A tourniquet was inflated to a pressure of 350 mmHg before the incision. The tourniquet was not released until skin closure and the application of a compressive dressing. The postoperative rehabilitation program included the continuous passive motion of the knee and muscle strengthening exercise after returning to the ward and routine mobilization on the first POD. The criteria for discharge were a clean wound without discharge and the ability to walk with walker support. This particular regimen was chosen to promote greater compliance with postoperative anticoagulation after the introduction of rivaroxaban guidelines and to avoid early postoperative minor and major bleeding complications of rivaroxaban. Demographic data and details of inpatient admission were obtained. Data comprised comorbidities, medication history, operative records, blood results, and thromboprophylaxis management also. The randomization concluded with similar demographic characteristics (age, BMI, the severity of osteoarthritis, knee angle deformation, ASA) (Table 1). The follow-up period began on the first postoperative day until the last postoperative follow up, two months postoperatively for all patients.

The patients were visited after the admission and data preoperatively and postoperatively were included: Hb levels, hematocrit (Hct) levels, prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count. The data during hospital stay were collected two times postoperatively and at two, four and eight weeks postoperatively. Prevalence of seven primary outcomes during rivaroxaban treatment was investigated: imaging confirmed symptomatic pulmonary embolism (PE), imaging-confirmed symptomatic DVT, myocardial infarction (MI), stroke, death, major bleeding episodes (MBE), and non-major bleeding episodes (NMBE). The primary efficacy outcome was preventing symptomatic or ultrasonography/triplex-proven DVT or associated PE for two months after surgery. All patients were evaluated for DVT with ultrasound/triplex in clinical suspicion after surgery by the same radiologist. The safety outcome was the knee arthroplasty incidence of bleeding during the thromboprophylaxis period. Bleeding events were defined as major or minor (non-major) according to previous studies [14]. “Major bleeding” was defined in accordance with recommendations from the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis as a bleed that was fatal, occurred in a critical area or organ, resulted in a fall in haemoglobin of ≥ 20 g/l, required at least two units of blood transfusion, or a surgical-site bleed necessitating return to theatre for open, arthroscopic or endovascular intervention [13]. Minor bleeding includes skin hematoma of ≥ 25 cm², wound hematoma ≥ 100 cm², spontaneous nose or gingival bleeding lasting more than 5 minutes, spontaneous rectal bleeding creating more than a spot, spontaneous macroscopic hematuria or hematuria lasting more than 24 hours in presence of the urinary catheter. “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 two groups were similar. No DVT or PE events were observed after clinical and ultrasound/triplex evaluation of the patients during the hospitalization period and at the follow-up. During the hospitalization period, one minor bleeding (wound hematoma) was observed at the first group (rivaroxaban), and one minor bleeding (skin hematoma) at the second group (enoxaparin/rivaroxaban) (Table 2). No major bleeding events were reported during the hospital stay and outpatient period in any group. There were no statistically significant differences in the total number of minor bleeding events and outpatient bleeding events among the two groups ($p > 0.05$). There was no statistically significant difference between complication rates and thrombosis-related events among the groups; however, the number of patients in the study is not sufficient to extrapolate our results to the general population.

	Group A (RIVAR/TRX)	Group B (LMWH-RIV/TRX)
Blood loss (Redon 48h) (cc)	440	511
Lower Hct/Hb	28.6/9.3	29.1/9.7
Dismission Hct/Hb	30.2/10.1	31.8/10.8
Trasfusions	0	0
Minor Bleeding during hospitalization	1	1
Major Bleeding during hospitalization	-	-
Outpatient care Minor/Major Bleeding	-	-

Table 2: Blood loss Measurements.

Abbreviations: TRX: Tranexate Acid; RIV: Rivaroxaban; LMWH: Low Molecular Weight Heparin.

Discussion

As stated above, the efficacy of new oral anticoagulants is clearly proven with phase-III randomized controlled studies. The effectiveness and safety of rivaroxaban in major orthopedic surgery were maintained irrespective of the administration time of the first postoperative dose within 24 hours postoperatively, the type of anesthesia, and the additional use of mechanical thromboprophylaxis [11].

The higher efficacy of new oral anticoagulants is generally associated with a higher bleeding tendency in patients undergoing total joint replacement. The risk of relevant bleeding is higher with rivaroxaban than with enoxaparin and the same tendency exists also vs dabigatran [10]. Rivaroxaban was more beneficial than enoxaparin for preventing symptomatic DVT but increased the risk of major bleeding [5]. In the RECORD studies, rivaroxaban resulted in greater benefits than harms compared with enoxaparin regarding symptomatic venous thromboembolism, and major bleeding. When incorporating surgical-site bleeding, rivaroxaban also results in greater benefit than harm for TKA and is balanced with enoxaparin for THA [2]. Lazo-Langner, *et al.* reported that rivaroxaban was associated with a lower risk of hospitalization due to DVT than low molecular weight heparin, with no significant difference in hospitalizations for major bleeding [15]. Levithan, *et al.* in risk-benefit assessment study, reported that rivaroxaban compared with enoxaparin therapy after joint arthroplasty, resulted in more benefits and less adverse events, with benefits exceeding adverse effects, starting immediately after initiation of therapy through long-term follow-up [2]. New oral anticoagulants are new alternatives to enoxaparin for DVT prophylaxis after TKA and have a proven safety profile, but their associated bleeding tendency makes enoxaparin first-choice prophylaxis choice. In switch-therapy modalities, we take advantage of enoxaparin safety during the hospitalization period and compliance of new oral anticoagulant drugs during the outpatient period. Loganathan *et al.* described the necessity and effectiveness of rivaroxaban if used in a modified regimen involving enoxaparin administered in the inpatient setting followed by rivaroxaban upon hospital discharge [16]. Turhan Özler, *et al.* also reported the enoxaparin advantage of safe administration during the hospitalization period and ease of use of new oral anticoagulant drugs during the outpatient period [17].

In the current study, we did not observe an increased or decreased bleeding rate in the switch-DVT prophylaxis regimen (enoxaparin during the hospitalization period and rivaroxaban during the outpatient period) in the hospitalization period neither the outpatient follows up. The switch-DVT-prophylaxis treatments were equally safe and efficient compared to rivaroxaban monotherapy. The advantages of enoxaparin regimen during inpatient stay was the familiar use and manageable possible complications to the medical and nursing team, whereas switching to rivaroxaban upon hospital discharge meant patients could self-administer rivaroxaban conveniently, with better and safer prophylactic compliance. We believed that our different conclusion to previous authors is due to the advantage of controlling major and minor bleeding by combined tranexamic acid administration intraoperatively (intravenous and intraarticular), as reported by other studies [18]. The weakness of the current study was the small sample size. Future studies are needed with larger sample sizes we can understand the reliability of the current kind of switch-therapy modality.

Conclusion

The advantage of using switch modified regimen (enoxaparin to rivaroxaban) for chemoprophylaxis after total knee arthroplasty exists and are equally safe and efficient as the rivaroxaban monotherapy when protocol of blood transfusion control is followed.

Disclosure

The authors declare that they have no competing interests and any conflicts of interest financial or otherwise, with individuals or organizations that could influence the author's work inappropriately. The authors disclose any actual or potential conflict of interest and all patients taking part of this study consent to use all the necessary data from their medical files for the study. A written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

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