EFFICACY AND SAFETY OUTCOMES OF RIVAROXABAN IN ACUTE DEEP VENOUS THROMBOSIS PATIENTS

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Abstract

Background

Rivaroxaban is the first oral anticoagulant drug that is a direct inhibitor of activated factor X (FXa) of clotting which may provide a simple, fixed-dose regimen for treating acute deep-vein thrombosis (DVT) without the need for laboratory monitoring.

Method

An opened label randomized parallel group clinical trial compared subcutaneous enoxaparin 1 mg/ kg once daily for 5 days followed by oral rivaroxaban 20 mg once daily with subcutaneous enoxaparin 1 mg/ kg once daily followed by a vitamin K antagonist (warfarin) for 2 month of treatment. The primary efficacy outcome for both was recurrent venous thromboembolism (VTE). The principal safety outcome was major bleeding or clinically relevant non major bleeding.

Results

Out of the 20 patients in the rivaroxaban group, 5 patients (25%) developed bleeding events while in the standard therapy group 8 out of 20 patients, 40 % developed bleeding events. Moreover, 10 patients in the rivaroxaban group (50%) developed adverse drug reactions versus 14 patients (70%) in the standard therapy group. However, none of the patients in both groups developed recurrent VTE neither DVT nor pulmonary embolism (PE).

Conclusion

Enoxaparin at dose of 1 mg/ kg followed by rivaroxaban at a dose of 20 mg once daily is effective, safe and well tolerated drug treatment option for patients with DVT.

Introduction:

Deep vein thrombosis (DVT) and acute pulmonary embolism (PE) are two manifestations of the same disorder, venous thromboembolism (VTE). **Venous thromboembolism** affects 1 to 2 adults per 1000 annually and is the third most common cause of vascular death after myocardial infarction and stroke **(Oger, 2000).**

Although its exact incidence is unknown, nearly 1 million cases (incident or recurrent, fatal and nonfatal events) occur in the United States each year **(Heit, 2008)**. Approximately 2 million patients are diagnosed with **deep venous thrombosis (DVT)** each year **(Geerts et al., 2004).** Even in the absence of pulmonary embolism (PE), DVT may cause significant morbidity resulting from chronic swelling, ulceration, debilitating pain, and future risk of recurrent DVT and PE **(Hirsh and Hoak, 1996)**.

A thrombus in the deep venous system of the leg is not dangerous in itself. The situation becomes life-threatening when a piece of the blood clot breaks off travels downstream through the heart into the pulmonary circulation system, and becomes lodged in the lung. Diagnosis and treatment of DVT is meant to prevent pulmonary embolism **(Goldhaber et al., 1999)**. Also post-phlebitic syndrome can occur after a deep vein thrombosis (the affected leg can become chronically swollen and painful with skin color changes and ulcer formation around the foot and ankle) (**Kahn and Ginsberg, 2004**). Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively **(Wells et al., 2000)**.

The current standard treatment for many patients with DVT is rapidly acting parenteral anticoagulants (low molecular weight heparin, unfractionated heparin or fondaparinux) for 5 to 7 days overlapped with at least 3 months of treatment with a vitamin K antagonist (warfarin) **(Guyatt et al., 2012).**

Recently, a number of new oral and parenteral anticoagulants have been developed with the aim of overcoming some of the drawbacks of warfarin and the other currently available agents, and to improve the prevention and treatment of thromboembolic disorders. **Rivaroxaban** is the first oral anticoagulant drug that is a direct inhibitor of activated factor X (FXa) of clotting. This inhibition disrupts the intrinsic and extrinsic pathways of coagulation cascade, inhibiting therefore the formation of thrombin and thrombus formation. Rivaroxaban is well absorbed from the gut and maximum inhibition of factor Xa occurs four hours after a dose. The effects last 8–12 hours, but factor Xa activity does not return to normal within 24 hours so once-daily dosing is possible **(Mueck et al., 2014)**.

Rivaroxaban demonstrated similar efficacy to warfarin for the treatment of acute VTE and prevention of recurrent VTE in large prospective randomized controlled trials **(Bauersachs et al., 2010; Buller et al., 2012).** These studies demonstrate that oral rivaroxaban has similar efficacy to conventional anticoagulation as a primary therapy for DVT and PE, without an increased risk of bleeding. Therefore, the aim of the present study was to compare efficacy and safety of enoxaparin / rivaroxaban versus standard therapy on management of patients with acute DVT.

Study Design

This study was an opened label randomized parallel group clinical trial. The study was conducted at Ain Shams University Hospitals (ASUH) Vascular surgery department from June 2012 till December 2013.

Patients

All patients presenting to the department of vascular surgery at ASUHs and diagnosed with acute DVT were assessed for eligibility criteria. Patients were eligible if they were in the age range from18 to 65 and recently diagnosed with lower extremity DVT by

Duplex. Patients were ineligible to participate if they had renal disorder, clinically hepatic disorder and clinically significant active bleeding.

Patients who fulfilled the inclusion criteria were included and randomized to one of two groups; the first group was of twenty patients who received enoxaparin 1mg/Kg by subcutaneous injection for at least 5 days in conjunction with dose adjusted oral warfarin. Once the target INR was reached enoxaparin was discontinued and the patients continued on dose adjusted oral warfarin once daily for two months while the second group was of twenty patients who received enoxaparin 1mg/Kg by subcutaneous injection for at least 5 days followed by oral rivaroxaban at a fixed dose of 20 mg once daily for two months.

Ethical Consideration:

A written informed consent was obtained from each of the participants before recruitment in the study. Patients who refused to sign the informed consent were excluded from this study. The study design was approved by the local Ethics Committee Review Board at Faculty of Pharmacy, Ain Shams University, Egypt.

Methods:

All patients were assessed at baseline by the physician and the clinical pharmacist for full medical history including their age, sex, co-morbid diseases and risk factors of DVT, medication history and clinical assessment. Clinical pharmacist assessed patients weekly for two months for efficacy outcomes including incidence and severity of thromboembolic complications such as recurrent DVT or PE and safety outcomes including incidence and severity of bleeding episodes (major or minor). Moreover patients were assessed for other adverse drug reactions to the use of rivaroxaban or warfarin such as diarrhea, constipation, nausea, heart burn, dizziness, vomiting, back pain, abdominal pain, edema, headache, rash, fever, pain, hypotension and night sweating.

Statistical analysis:

Data were collected, revised, verified then edited on personal computer. Statistical analysis was performed using SPSS software (statistical package for the social sciences, version 21, SPSS Inc., Chicago, IL, USA). Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test.

Results

Safety and Efficacy outcomes

Patient demographics & clinical characteristics were comparable in both groups except for gender and white blood cells (WBCs) as shown in table (1).

Table 1: demographic data & Clinical characteristics

Characteristic	Rivaroxaban (N=20)	Standard (N=20)	P-value
Male Sex	14 (70 %)	7 (35%)	0.027
Age (Yrs), mean ± SD	50.90 ± 9.23	49.00 ± 10.29	
Complete Blood count as mean ± SD			
Red blood cells (RBCs)	4.42 ± 0.67	4.52 ± 0.43	0.396
Hemoglobin	12.62 ± 2.24	12.33 ± 1.58	0.285
Hematocrit	39.23 ± 5.70	37.15 ± 5.32	0.046
MCV	88.75 ± 6.77	83.28 ± 6.82	0.117
MCH	28.09 ± 2.96	28.56 ± 3.27	0.812
MCHC	31.95 ± 2.39	32.60 ± 1.71	0.403
White blood cells (WBCs)	7.25 ± 1.54	9.15± 2.60	0.016
Platelets Median Interquartile range	278.5 (174.00 445.00)	298 (83.00-408.00)	P = 0.507

Out of the 20 patients in the rivaroxaban group, 5 patients (25%) developed bleeding events while in the standard therapy group 8 out of 20 patients, 40 % developed bleeding events. The overall bleeding incidence was numerically lower; but not significantly lower (P = 0.311) in patients receiving rivaroxaban than those receiving standard therapy as shown in Figure (1).
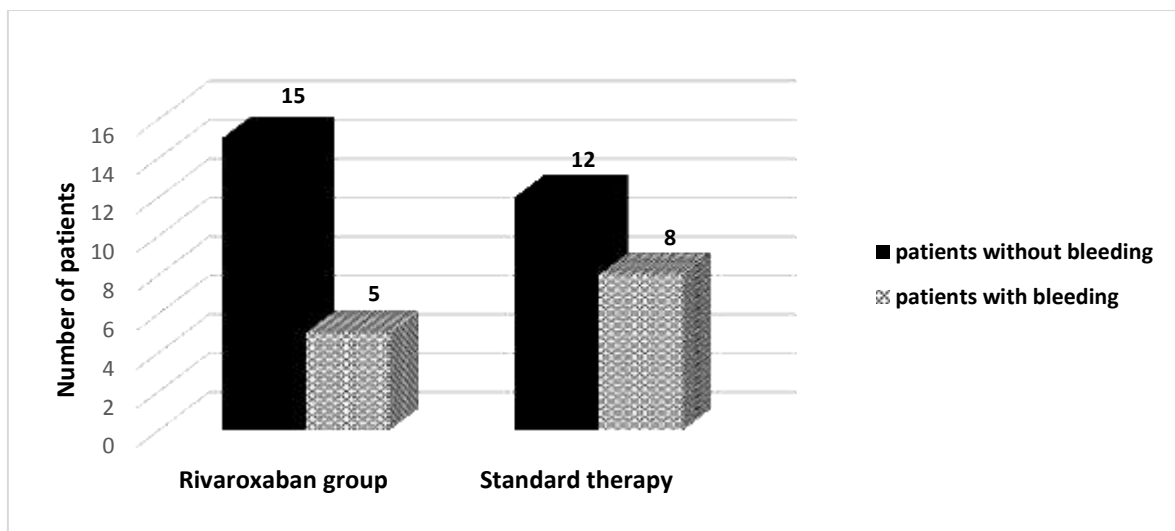

Figure 1: Overall bleeding incidence in Rivaroxaban group versus Standard therapy group

Moreover, 10 patients in the rivaroxaban group (50%) developed adverse drug reactions versus 14 patients (70%) in the standard therapy group. Therefore, the overall incidence of ADRs was numerically lower; but not significantly lower (P value = 0.197) in patients receiving rivaroxaban than those receiving standard therapy as shown in Figure (2).

Laboratory evaluation

After 8 weeks of follow up there was no significant difference between rivaroxaban group and standard therapy group in blood profile including RBCs count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets count and WBCs count as shown in table (2).
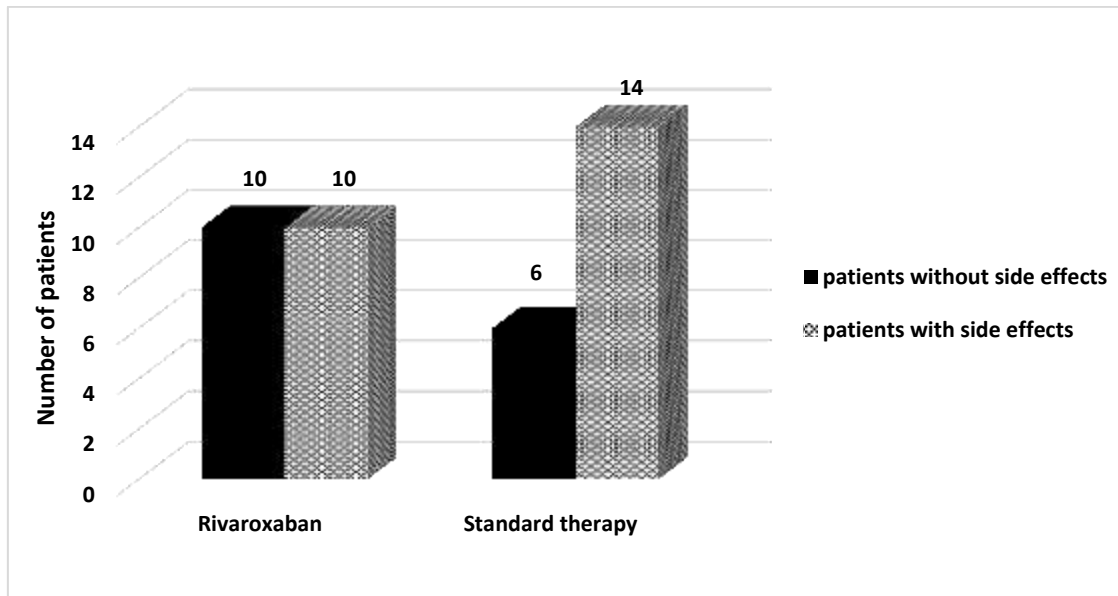

Figure 2: Overall adverse drug reactions (ADRs) incidence in Rivaroxaban group versus Standard therapy group

However, none of the patients in both groups developed recurrent VTE neither DVT nor PE. The overall incidences of recurrent VTE were similar in patients receiving rivaroxaban and those receiving standard therapy.

Table 2: Laboratory evaluation after 8 weeks

Characteristic	Rivaroxaban (N=20)	Standard Therapy (N=20)	P-value
Complete Blood count as mean ± SD			
Red blood cells (RBCs)	4.70 ± 0.46	4.52 ± 0.43	0.237
Hemoglobin	13.21 ± 1.97	12.71 ± 1.74	0.059
Hematocrit	40.91 ± 3.88	38.66 ± 4.11	0.102
MCV	87.55 ± 6.94	85.74 ± 5.25	0.131
MCH	28.19 ± 3.38	28.25 ± 2.76	0.686
MCHC	32.19 ± 3.24	32.91 ± 1.85	0.652
White blood cells (WBCs)	7.69 ± 1.73	9.30 ± 3.0	0.38
Platelets Median	276	287	P = 0.807
Interquartile range	(173.00 -445.00)	(126.00-428.00)	

Discussion

According to guidelines published by American Collage of Chest Physicians (ACCP) the current standard treatment for many patients with DVT is rapidly acting parenteral anticoagulants (low molecular weight heparin, unfractionated heparin or fondaparinux) for 5 to 7 days overlapping with a vitamin K antagonist (warfarin) for at least 3 months of treatment (**Kearon et al., 2012**). In 2012 the FDA approved rivaroxaban for the treatment of acute DVT. The present study shows that rivaroxaban is as effective as standard therapy, with similar safety, for the treatment of acute DVT. The overall incidences of recurrent VTE and bleeding events were similar in patients receiving rivaroxaban and those receiving standard therapy. In agreement with *Agnelli, et al.* study which showed that oral rivaroxaban at a dose of 15 mg twice daily for 3 weeks followed by 20 mg once daily for 3 month has non-inferior and possibly superior efficacy and similar safety profile in terms of major and non-major bleeding compared to standard therapy in the treatment of patients with acute deep venous thrombosis. Moreover, *Eriksson, et al.* **2008 and** *Lassen, et al.* **2008** showed that oral rivaroxaban (10 mg) once daily has non-inferior and possibly superior efficacy compared to subcutaneous enoxaparin 40 mg once daily with similar safety profiles including low rates of major bleeding in preventing VTE in adult patients undergoing total hip or knee replacement surgery. However, *Cohen, et al.* **2013** showed that taking rivaroxaban 10 mg once daily for 35 days was associated with a significant increase bleeding rates, compared with standard 10-day treatment with enoxaparin 40 mg by subcutaneous injection, in acutely ill medical patients.

Conclusion:

No notable differences were found during the 2 month of follow up regarding the incidence of subsequent recurrent VTE, bleeding and adverse drug reactions in patients treated with rivaroxaban than those receiving standard therapy. In conclusion,

the present study showed that rivaroxaban at a dose of 20 mg once daily is effective, safe and well tolerated drug treatment option for patients with DVT.

Recommendations:

Future studies should be conducted for a longer duration to assess the long-term efficacy, safety and coagulation profile changes of rivaroxaban in deep venous thrombosis patients. Finally, more data are required on the optimal management of major bleeding events and on the management of patients requiring urgent invasive procedures.

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الملخص العربي

فاعلية و سلامة عقار الريفاروكسابان في مرضى التجلط الوريدي العميق المزمن

للسادة الدكاترة

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الجلطات الدموية الوريدية تؤثر على 1-2 من كل ١٠٠٠ من البالغين سنويا و يتم العلاج عن طريق الحقن بمضادات التخثرالسريعة بالأضافة إلى مضاد فيتامين ك. الريفاروكسابان هو أول عقار مضاد عامل التخثر Xaعن طريق الفم .

الهدف من البحث:

تقييم تأثيرات عقار الريفاروكسابان مقابل عقار الوارفارين على المعدلات التالية: خطر حدوث مضاعفات الانسداد التجلطي وخطر حدوث الجلطات الدموية الوريدية المتكررة و خطر حدوث النزيف الرئيسي والثانوي .

المرضى و الطرائق:

و قد أجريت هذه الدراسة على ٤٠ مريضا مصابا بالتجلط الوريدي العميق تلقوا عقار الإينوكسابارين عن طريق الحقن تحت الجلد لمدة لا تقل عن 5 أيام حتى يتم الوصول إلى مستوى الأي أن أر العلاجي (٢-٣)، تم تقسيم المرضى بعشوائية إلى مجموعتين: **المجموعة الأولى:** تتألف من عشرين مريضا تلقوا عقارالوارفارين عن طريق الفم مرة واحدة يوميا لمدة شهرين. **المجموعة الثانية:** تتألف من عشرين مريضا تلقوا عقار الريفاروكسابان 20 ملغ عن طريق الفم مرة واحدة يوميا لمدة شهرين.

النتائج :

أظهرت الدراسة أن المعدل العام من الجلطات الدموية الوريدية المتكررة مماثل في كلتا المجموعتين. كما لا توجد فروق ملحوظة في كلا من المعدل العام من حدوث نوبات النزيف و المعدل العام من حدوث تفاعلات دوائية معاكسة في المرضى الذين يتلقون عقارالريفاروكسابان (25%)، (50%) وأولئك الذين يتلقون الوارفارين (70%)، (40%) على التوالي.

الاستنتاجات:

لا توجد فروق ملحوظة بين عقار الريفاروكسابان و عقار الوارفارين بشأن حدوث الجلطات الدموية الوريدية المتكررة و خطر حدوث النزيف الرئيسي والثانوي و التفاعلات الدوائية المعاكسة مما يثبت سلامة و فاعلية عقار الريفاروكسابان .