

EVALUATION OF NEW ORAL ANTICOAGULENTS IN MANAGEMENT OF DEEP VEIN THROMBOSIS

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ABSTRACT

Background: Low molecular weight heparin (LMWH) and vitamin K antagonists (VKAs) have been considered the first line option for the prevention and treatment of venous thromboembolism (VTE) for several years after decades during which warfarin was the only oral anticoagulation option; newer anticoagulants have the potential to change the management of coagulation disorders. The new oral anticoagulants (NOACs) differ from VKAs in their action mechanism because of direct inhibition of proteins of the coagulation cascade. They have more predictable pharmacokinetics leading to fixed and convenient dosing regimens and no need for routine monitoring, as well as in a rapid onset of action, and importantly, high efficacy and low risk of bleeding. Some of their limitations are the higher cost, limited monitoring (if needed, as only qualitative measures available) and the lack of a specific antidote.

Objectives: To evaluate the efficacy and side effects of the new groups of oral anticoagulants in comparison to traditional oral anticoagulants in management of deep vein thrombosis.

Patient and methods: This work was done over 50 patients, divided into 2 equal groups: Group I received oral rivaroxaban for 3 months, and group II received warfarin guided with INR measurement for 3 months. The following was done for all patients: Complete blood count, coagulation profile, liver function tests, kidney function tests and duplex scan.

Results: Rivaroxaban (group I) included 9 males and 16 females with a mean age of 37.6 (27-60), and a mean body weight of 83.7 ± 16.3 . Warfarin group II included 7 males and 18 females with a mean age of 37.9 (27-52), and a mean body weight of 84.2 ± 13 . The main symptoms of our patients were leg pain in 86%, leg swelling in 78%, tenderness in 74%, redness/warmth in the leg in 34%, the main risk factors for DVT were hormonal contraceptive in 44%, immobilizations in 34%, hypercoagulability in 30%, operative history in 24%, history of orthopedic surgery in 22%, old age in 8%, with no statistical significant differences between the 2 arms of the study.

Conclusion: Rivaroxaban have the advantage of more predictable anticoagulation, fewer drug interactions, and vascular outcomes compared with warfarin. New oral anticoagulants have shown to have a favorable balance between efficacy and safety compared with warfarin because recanalization occurred, with high percentage in new oral anticoagulants more than warfarin. Rivaroxaban has a rapid onset of anticoagulant that can be given in fixed doses without routine monitoring.

Keywords: New oral anticoagulants, vitamin K antagonists, venous thromboembolism.

INTRODUCTION

Thromboembolic diseases are of major clinical concern due to their high

prevalence and consequences which are often fatal. VTE is a condition that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).

VTE may be provoked by identifiable clinical risk factors such as surgery, trauma, immobility, cancer, or occur in the absence of these risk factors "unprovoked VTE" (Wells et al., 2014). Treatment of venous and arterial thrombotic phenomena represents a major medical challenge, and the development of anticoagulant drugs represents a revolution in medicine.

During the last 60 years, VKAs which include coumarin derivatives, e.g. warfarin and acenocoumarol, have been the only oral anticoagulants used. However, new substances with anticoagulant effects, referred to as new oral anticoagulants, have been discovered. Compared with VKAs, this new generation of oral anticoagulants (non-vitamin K antagonist oral anticoagulants, NOACs) has more predictable anticoagulant responses, and NOACs have been shown to be effective in the prevention and treatment of VTE and in the prevention of stroke (Holy and Beer, 2013).

Once the diagnosis of VTE has been made, antithrombotic therapy should be initiated promptly. If clinical suspicion for VTE is high, it may be prudent to start treatment, while the diagnosis is objectively confirmed. The goals of VTE treatment are the prevention of mortality and morbidity associated with PE and the prevention of the postthrombotic syndrome (Brunicardi et al., 2014).

The NOACs differ from VKAs in their action mechanism because of direct inhibition of proteins of the coagulation cascade. They have more predictable pharmacokinetics leading to fixed and convenient dosing regimens and no need

for routine monitoring, as well as in a rapid onset of action and, importantly, high efficacy and low risk of bleeding. Some of their limitations are the higher cost, limited monitoring (if needed, as only qualitative measures available), and the lack of a specific antidote (Miesbach and Seifried, 2012).

The NOACs fall into two broad categories: direct thrombin inhibitors (Dabigatran) and the factor Xa inhibitors (Rivaroxaban and Apixaban) (Brieger, 2014).

The present work aimed to evaluate the efficacy and side effects of new groups of oral anticoagulants in management of DVT.

PATIENTS AND METHODS

This was a prospective study including fifty patients presented clinically with DVT, and the diagnosis confirmed by color-coded duplex scan, has been the material of this study. Those patients were followed up in Al-Azhar University Hospital (Sayyed Galal Hospital), and Al Agouza Hospital, from March 2016 till December 2016. The patients were randomly allocated into 2 equal groups:

- **Group I:** Patients were given the new oral anticoagulation (Rivaroxaban) regimen for DVT. Rivaroxaban 15 mg was given twice daily for 21 days, followed by 20 mg once daily for 3 months duration, and follow up for another 3 months .
- **Group II:** Patients were given the usual full anticoagulation regimen of DVT in the form of Warfarin. Most of patients started on 5mg daily to an INR of 2.0–3.0 for 3 months duration, and follow up for another 3 months.

Inclusion criteria:

1. Age \geq 18 years.
2. Clinical and radiological diagnosis of DVT.

Exclusion Criteria:

1. Active bleeding or high risk for serious bleeding.
2. Recent stroke.
3. Uncontrolled high blood pressure.
4. Significantly impaired kidney function.
5. Recent (< 3 Months) gastrointestinal (GI) bleeding, active peptic ulcer and severe liver dysfunction.
6. Recent trauma or surgery.
7. Patients suspected pulmonary embolism.
8. Allergy to heparin and enoxaparin.
9. Hemoglobin < 9.0 mg/dl.

Anticoagulation medication doses were adjusted according to the follow up. Patients were asked to attend the outpatient clinic at fixed intervals, i.e after 1 month, 3 months, and 6 months of the acute phase. At each occasion, a physical examination as well as a duplex scan was performed and recorded for each patient. The INR value was determined weekly in the 1st month and at least monthly thereafter, or at any time considered necessary. Blood samples were collected for the measurement of full blood count, liver function test, coagulation tests, INR values, and renal function test. Complications and side effects were noted.

The assessment of each patient included registration of detailed medical history, clinical examination, blood tests,

and color duplex scan. To obtain a detailed personal and familial medical history, a special protocol form was filled in by each patient. This was based on the questionnaires and physical examination, which included the most specific symptoms and signs as well as the main risk factors of DVT. Clinical signs of pulmonary embolism or any complications were also assessed. Laboratory investigations included complete blood count, urea, creatinine, liver function tests, and coagulation profile.

Written consents were obtained from all patients before participating in this study after explaining all aspects of this study.

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program version 13.0, SPSS Inc., Chicago, Illinois, USA for statistical analysis. Data entered as numerical or categorical, as appropriate. Quantitative data were shown as mean, SD, and range. Qualitative data were expressed as frequency and percentage. Statistical analysis was done using Chi-square test for qualitative data and two sample t-test for quantitative data. P (probability) value will be considered to be of statistical significance if it was less than 0.05.

RESULTS

Rivaroxaban (group I) included 25 patients 9 males and 16 females with a mean age of 37.6 (27-60) and a mean body weight of 83.7 ± 16.3 . Warfarin group II included 25 patients 7 males and 18 females with a mean age of 37.9 (27-52) and a mean body weight of 84.2 ± 13 (Table 1).

Table (1): Demographic data of studied groups.

Parameters \ Drugs	Rivaroxaban	Warfarin	Total	P-Value
Sex, n (%)				
Male	9 (56.25)	7 (43.75)	16 (32)	> 0.05
Female	16 (47.05)	18 (52.94)	34 (68)	> 0.05
Age (years)				
Mean (range)	37.6±8.63 (27-60)	37.9±7.35 (27-52)	37.78 (27-60)	> 0.05
Body weight (Kg)	83.7± 16.3	84.2± 13	83±14	> 0.05

The main symptoms of our patients were leg pain in 86%, leg swelling in 78%, tenderness in 74%, redness/warmth in the leg in 34% (Table 2).

Table (2): Symptoms of DVT in the studied patients.

Symptoms \ Count	No	%
Leg pain	43	86
Leg swelling	39	78
Tenderness	37	74
Redness/Warmth in the Leg	17	34

The main risk factors for DVT were hormonal contraceptive in 44%, immobilizations in 34%, hypercoagulability in 30%, operative history in 24%, history of orthopedic surgery in 22%, and old age in 8% (Table 3).

Table (3): Risk factors of DVT of studied patients.

Risk factors \ Count	No	%
Operative history	12	24
Old age	4	8
History of orthopedic surgery	11	22
Hypercoagulability	15	30
Contraceptive	22	44
Immobilizations	17	34

The recorded side effects were bleeding in two cases of group I and three cases of group II, headache in one case of group I and two cases of group II, diarrhea in one case of group I and two cases of group II, constipation in two cases of group I and one case of group II, nausea in one case of group I and two cases of group II, vomiting in one case of group I

and one case of group II, abdominal pain in one case of group I and two case of group II, dizziness in one case of group I and two cases of group II, overall side effects incidence in rivaroxaban group 10 patients, while overall side effects incidence in warfarin group 15 patients (Table 4).

Table (4): Statistical comparison of the side effects of group I (Rivaroxaban) against group II (Warfarin).

Groups	Group I (Rivaroxaban) (n=25)	Group II (Warfarin) (n=25)	P-Value
Side effects			
Overall incidence (n) (%)	10(40%)	15(60%)	1.000
Mean ± SD	12.50±4.95	12.50±9.19	

Out of the 25 patients in the standard therapy group, 1 patient (4%) showed no recanalization of the affected veins, 9 patients (36%) showed recanalization of some of the affected veins, 15 patients (60%) showed recanalization of all of the

affected veins. In the rivaroxaban group; 8 patients (32%) showed recanalization of some of the veins and 17 patients (68%) showed recanalization of all of the affected veins (Table 5).

Table (5): Over all incidence of recanalization in Rivaroxaban group, versus standard therapy group.

Drugs	Group I (Rivaroxaban) (n=25)	Group II (Warfarin) (n=25)	P-Value
Recanalization			
No recanalization	0	1	> 0.05
Recanalization of some veins	8	9	
Recanalization of all veins	17	15	
Mean ± SD	2.560±0.712	2.520±0.653	

INR and PT were significantly lower in the rivaroxaban group rather than the standard therapy group while in PTT there Table (6): Coagulation profile assessment.

was no significant difference between both groups (Table 6).

Drugs Parameters	Rivaroxaban group	Standard therapy group	P-Value
INR	1.22 ± 0.1349	2.66 ± 0.2498	0.0001
PT	16.7 ± 1.239	13.28 ± 1.285	0.0001
PTT	32.78 ± 0.99	32.47 ± 0.79	> 0.05

DISCUSSION

VKAs have a slow onset of activity and must be monitored regularly so that the dose can be adjusted to ensure that the protective effect is combined with an acceptable risk of bleeding. Monitoring is done by the determination of the prothrombin time, which is converted into the international normalized ratio. Effective therapy for VTE is reflected by an INR of 2.0-3.0, whereas an INR >3 results in more bleeding without any benefit in the prevention of recurrent thrombotic episodes (**Barnes et al., 2015**).

The effort of routine coagulation monitoring is costly, makes patient care complex, and is a considerable burden on the patients' life during long term therapy. Present long-term therapy recommendations by the American College of Chest Physicians are that patients with reversible or time-limited factors should be treated for at least 3 months, patients with symptomatic isolated calf vein thrombosis for at least 6-12 weeks, and patients with a first episode of VTE without a known risk factor (idiopathic VTE) for at least 6 months. Finally, in patients with recurrent idiopathic VTE or continuing risk factors such as cancer, antithrombin-deficiency, or anti-phospholipid antibody syndrome (APA), treatment for 12 months or longer

is recommended (**Eikelboom and Weitz, 2010**).

Our study showed that rivaroxaban administration in acute DVT was associated with lesser occurrence of drug interaction, and warfarin needed dose adjustment versus rivaroxaban. Rivaroxaban was comparable to warfarin in the occurrence of bleeding and recanalization. The warfarin group showed a significantly higher increase in INR and PT versus Rivaroxaban.

In our study, 8 % of the rivaroxaban group developed bleeding versus 12% of the standard therapy group. Yet, this difference was not statistically significant. Similarly, **Abd Alwahab et al. (2015)** showed no significant difference between rivaroxaban (10%) and standard therapy (11%) in bleeding incidences.

In the current study, the percentage of adverse drug reactions was numerically lower in the rivaroxaban group versus the standard therapy group. These results were consistent with the results of recorded study which showed that adverse drug reactions occurred in 12.2% of patients given rivaroxaban versus 11.9% of patients given enoxaparin. Yet, the differences were not statistically significant indicated that rivaroxaban was comparable and a tolerable alternative to

standard therapy with non-remarkable adverse drug reactions (**Lassen et al., 2012**).

Our study showed that more patients in the standard therapy group (20%) required therapy discontinuation versus those in the rivaroxaban group (16%). In Einstein DVT study, patients in the rivaroxaban group who required therapy discontinuation were 13 versus 14.2 and 12.3 % in the standard therapy group respectively (**Angelli et al., 2010 and Buller et al., 2012**). Moreover, in another study, only 3% of patients dropped out the treatment due to medical reasons (**Jara Palomares et al., 2014**). In agreement with our results, **Agnelli et al. (2007)** reported a good adherence to rivaroxaban in 94% of patients.

Regarding the need for dose adjustment, our study showed that none of the patients in the Rivaroxaban group required dose adjustments, as compared to patients in the standard therapy group required dose adjustments. Similarly, in the Einstein DVT trials in which Rivaroxaban was given at a fixed dose of 15 mg twice daily for three weeks followed by 20 mg once daily for 3 month, none of the patients required dose adjustment in the rivaroxaban group, while all patients in the standard therapy group required dose adjustment to achieve a therapeutic range (**Angelli et al., 2010 and Buller et al., 2012**). Moreover, findings of the study by **Kubitza et al. (2007)** showed that extremes of body weight (<50 kg or >120 kg) did not significantly influence rivaroxaban exposure and did not require dose adjustment.

CONCLUSION

Rivaroxaban have the advantage of more predictable anticoagulation, fewer drug interactions, and vascular outcomes compared with warfarin. However, the treatment benefits compared with warfarin have higher cost. New oral anticoagulants have shown to have a favorable balance between efficacy and safety compared with warfarin because recanalization occurred with high percentage in new oral anticoagulants more than warfarin. NOACs did not require monitoring or dose titration to achieve optimal anticoagulation, and have fewer food and drug interactions, shorter half-life and simpler dosing regimen.

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تقييم مضادات التخثر الفموية الجديدة في مناجزة جلطات الأوردة العميقة

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خلفية البحث: كان الوارفارين والهيبارين لعقود عدة هما الخط الأول للوقاية والعلاج من الجلطات، وظل الوارفارين خلال هذه العقود هو الخيار الوحيد لمنع تخثر الدم عن طريق الفم . وفي الآونة الأخيرة تم تطوير عددا من مضادات التخثر الفموية الجديدة وذلك بهدف التغلب علي بعض السلبيات من إستخدام الوارفارين. وتختلف مضادات التخثر الفموية الجديدة عن الوارفارين في آلية عملها عن طريق التنشيط المباشر للبروتينات من شلال التخثر. وتتميز بالبداية السريعة في العمل ، وتؤخذ بجرعات ثابتة لاتحتاج إلي المتابعة المستمرة أو تعديل الجرعات، والأهم من ذلك الفاعلية العالية وقلة وضعف حدوث النزف ، ويحد من إستخدامها عدم وجود ترياق محدد وإرتفاع التكلفة.

الهدف من البحث: تقييم الفاعلية والآثار الجانبية لمضادات التخثر الفموية الجديدة في مناجزة جلطات الأوردة العميقة في المرضى المصريين .

المرضي وطرق البحث: أجريت هذه الدراسة على خمسين مريضا يعانون من تخثر الأوردة العميقة بعد تأكيد التشخيص عن طريق المسح الضوئي . وتم تقسيم المرضى عشوائيا إلى مجموعتين متساويتين : تضم المجموعة الأولى المرضى الذين تلقوا عقار الريفاروكسيبان عن طريق الفم لمدة ٣ أشهر، وتضمنت المجموعة الثانية المرضى الذين تلقوا عقار الوارفارين مع قياس معدل الاي ان ار في الدم لمدة ٣ أشهر. وتضمنت متابعة المرضى إجراء تحليل صورة دم كاملة ، وقياس نسبة السيولة بالدم ، وزمن تركيز البروثرومبين ، وعمل وظائف كبد وكلي ، وعمل أشعة دوبلكس لجميع المرضى.

النتائج: شملت المجموعة الأولى ٩ ذكور و ١٦ إناث مع متوسط أعمار ٣٧,٦ (٢٧-٦٠)، ومتوسط وزن الجسم من ٨٣,٧ ± ١٦,٣. وتضمنت المجموعة الثانية ٧ ذكور و ١٨ إناث مع متوسط أعمار ٣٧,٩ (٢٧-٥٢)، ومتوسط وزن الجسم من ٨٤,٢ ± ١٣. وتم رصد أكثر الأعراض شيوعا ، كالآلم في الساق بنسبة ٨٦٪، وتورم الساق بنسبة ٧٨٪ ، وقابلية الإحساس بالآلم بنسبة ٧٤٪، ودفع وإحمرار الساق بنسبة ٣٤٪، وكانت عوامل الخطر الرئيسية للإصابة بجلطات الأوردة العميقة كوسائل منع الحمل الهرمونية بنسبة ٤٤٪، وقلة الحركة بنسبة ٣٤٪، وفرط التجلط بنسبة ٣٠٪،

والتاريخ الجراحي بنسبة ٢٤٪، وتاريخ جراحة العظام بنسبة ٢٢٪ والشيخوخة بنسبة ٨٪، مع عدم وجود فروق جوهرية في النتائج الإحصائية بين كل من المجموعتين في هذه الدراسة.

الإستنتاج: يتميز الريفاروكسيبان بالقدرة والفاعلية العالية في منع تخثر الدم ، وقلّة التفاعلات والتدخلات الدوائية إذا ما قورن بالوارفارين. وقد أظهرت الدراسة أن مضادات التخثر الفمية الجديدة أكثر فعالية وسلامة مقارنة مع الوارفارين ، واتضحت هذه الكفاءة والفاعلية في إذابة الجلطات وإختفاء درجة إنصمام الأوردة بنسبة عالية في مضادات التخثر الفمية الجديدة أكثر من الوارفارين. وتميز الريفاروكسيبان بالبداية السريعة في العمل ويؤخذ بجرعات ثابتة ومريحة ، ولايحتاج إلي المتابعة الروتينية أو تعديل الجرعات.