Rivaroxiban versus Warfarin in management of deep venous thrombosis (DVT)

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Abstract

Background: Venous thromboembolism (VTE), a disorder associated with a significant risk of morbidity and mortality, is composed of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Objectives: The aim of this study was to compare between rivaroxiban and warfarin regarding efficacy, safety and complications of treatment in patients with DVT.

Patients and methods: This is a randomized controlled clinical trial. From April 2021 to April 2022, seventy patients with DVT were diagnosed and followed up in Vascular Surgery Department in Qena University Hospital regarding clinical presentation and venous duplex ultrasonography scans. Studied patients were divided into two groups, Group A treated by rivaroxiban and Group B treated by warfarin. Comparison between variables of two groups was performed regarding efficacy, safety and complications of treatment.

Results: No significant differences between two groups were noticed regarding efficacy and clinical improvement while there was significant difference regarding bleeding as a complication e.g. bleeding in warfarin group as P value <0.05.

Conclusion: Rivaroxiban and Warfarin seem to have same efficacy regarding symptoms relief and prevention of DVT recurrence. Rivaroxiban is better than warfarin regadring bleeding risk, safety in all age groups, compliance and follow up as no need of laboratory monitoring**.**

Keyword: Deep vein thrombosis (DVT); Rivaroxiban; Warfarin.

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Introduction

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are both components of venous thromboembolism (VTE), which is a condition that is linked to a high risk of morbidity and mortality. Even though it has been widely believed for a number of years that warfarin is the most effective oral anticoagulant treatment for VTE, there are other options. Rivaroxaban is currently suggested by a number of clinical guidelines as either preferred to vitamin K antagonists (VKAs) or as an alternative to VKAs due to its superior safety profile with relation to bleeding. This is because rivaroxaban has a lower risk of adverse bleeding events **(Zirlik et al., 2017)**. There are many restrictions that apply to the clinical use of VKAs. Warfarin is a slow-acting drug that has a limited therapeutic range, can have unpredictable anticoagulant effects due to interactions with food and other medications, and has a metabolism that is very variable. It is necessary to do routine coagulation (laboratory) monitoring as well as dose adjustment in order to keep blood coagulation within the therapeutic window that is intended **(Haas et al., 2014)**.

Rivaroxaban is regarded a viable alternative to VKAs as conventional oral therapy for VTE due to the fact that it has a more quick onset and offset of action, fewer food and medication interactions, and predictable anticoagulant effects without the requirement for routine laboratory monitoring **(Kahn et al., 2014)**. In addition, the most recent VTE treatment guidelines promote rivaroxaban as a first-line alternative rather than warfarin, which is reflective of their rising use in clinical practise (**Kearon et al., 2017**).

Rivaroxaban was the first direct Factor Xa inhibitor that could be taken orally as a dosage. It does so in a way that is both direct and reversible with factor Xa. Rivaroxaban displays selectivity for Factor Xa over other comparable serine proteases that are greater than 10,000-fold. This selectivity allows it to inhibit Factor Xa in a competitive manner. In order for it to have an anticoagulant effect, it does not require any cofactors (like antithrombin, for example). Because of this activity, the coagulation cascade is unable to complete its journey along the last common pathway, which thwarts the production of thrombin. Both free-circulating and clot-bound versions of factor Xa are capable of biological activity.

(Bratsos et al., 2019). The aim of this study was to compare between rivaroxiban and warfarin regarding efficacy, safety and complications of treatment in patients with DVT.

Patients and methods

From April 2021 to April 2022, seventy DVT patients were diagnosed and followed up at Vascular Surgery Department in Qena University Hospital with signed informed consents for participation in the randomized controlled clinical trial study. The studied cases were divided randomly into two groups, Group A treated by rivaroxiban, while Group B treated by warfarin. Demographic characters of the patients were recorded and full risk factors assessment wasobtained.

Inclusion criteria: All patientswith recent DVT that had notreceived medication before who are attending vascular surgery outpatient clinic.

Exclusion Criteria: Patient with chronic DVT more than 1 year. 2- Patient with decompensated liver disease.Patient with large esophageal varices, Patient with a platelet count less than 50000 /mm³ which constitutes significant thrombocytopenia, patient with hypersensitivity to either drugs (Rivaroxiban& warfarin), patient with coagulation defects at baseline such that the INR is over 1.5 and patient with hypertension which is poorly controlled, or not under treatment.

History: Full medical history was obtained regarding age, sex, chronic diseases (diabetes, hypertension, cardiac condition, ESRD, ..), risk factors related to DVT as (cancer, bed ridden, CCPs, central lines, long travels, postpartum, ..) and complaint analysis regarding swelling, pain and its onset .

Clinical examination: All patients were examined with routine general examination and local vascular examination regarding:

edema (level, severity, pitting or not), hotness, tenderness, any dilated veins in the limb, pigmentations or scars and checking pulse.

Laboratory investigations: blood samples were collected for routine lab investigations including complete blood count (CBC), prothrombin time (PT), prothrombin concentration (PC), international normalizing ratio (INR) .Additionally, warfarin was monitored by INR to adjust dose and guarantee optimum therapeutic window and avoiding warfarin toxicity .Anti-FXa activity test wasn't used to monitor rivaroxiban as there were no cases recorded with bleeding during the study regarding group (A).

Imaging techniques: Venous duplex ultrasonography has been done to all cases as diagnostic tool at first time the patient has come to the vascular clinic and follows up method (1.5 months, 3 months and 6 months post DVT dignosis).DVT was classified according to the site of thrombosis to 3 types (iliac, femoral and calf veins thrombosis).

Management: In terms of the administration of warfarin, it was started on day 1 or 2 of the parenteral anticoagulation therapy (for example, LMWH or unfractionated heparin), and it was continued for at least 5 days until the required INR (>2.0) was maintained for 24 hours. , then parenteral therapy is discontinued, with the aim to maintain INR 2-3 for at least 3-6 months according to level of thrombosis and follow up duplex scan result.Regarding rivaroxiban management, it was imitated on day 1 in a dose of 15 mg twice per day for 21 days then the dose was adjusted to 20 mg once daily for 3-6 months at least.

Follow up: The two studied groups were followed up during the study duration regarding clinical improvement, serial venous duplex ultrasonography, laboratory investigations, compliance and complications (eg: bleeding and recurrence).

The current study has been approved by the Ethics Committe of Faculty of Medicine,SVU,Qena,Egypt, with ethical approval code : SVU-MED-VAS015-1-21-4-198 .

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 23.0; Armonk, NY). When the P value was less than 0.05, significance was determined. The Chi-square test was utilised in order to analyse the differences in proportions between the groups. When comparing the mean differences between the groups, an independent t-test was carried out.

Results

Patients were divided randomly into two groups according to drug administration:1) Group A (35 patients): given Rivaroxiban treatment.2) Group B (35 patients): given warfarin treatment (control group).

Table 1. Patients' demographic data and risk factors comparison between the two groups

Variables		Group A	Group B	P-value
Age in years		46.91 ± 18.16	50 ± 18.05	0.48
Gender	Male	11 (31.4%)	14 (40%)	0.45
	Female	24 (68.6%)	21 (60%)	
HTN	Yes	10 (28.6%)	18 (51.4%)	0.051
	No	25 (71.4%)	17 (48.6%)	
DM	Yes	9 (25.7%)	11 (31.4%)	0.597
	No	26 (74.3%)	24 (68.6%)	
Cancer	Yes	2 (5.7%)	2 (5.7%)	1
	No	33 (94.3%)	33 (94.3%)	
CCP	Yes	7 (20%)	6 (17.1%)	.79
	No	28 (80%)	29 (82.9%)	
Bed ridden	Yes	6 (17.1%)	5 (14.3%)	0.743
	No	29 (82.9 %)	30 (85.7 %)	
Central line	Yes	9 (25.7 %)	11 (31.4 %)	0.597
	No	26 (74.3 %)	24 (68.6 %)	
Idiopathic	Yes	11 (31.4 %)	13 (37.1%)	0.615
	No	24 (68.6 %)	22 (62.9%)	

* Chi-square test was used to compare proportions between groups.
* Independent t-test was used to compare the mean difference between groups.
* P value was considered statistically significant when < 0.05.

It was found that age, gender, chronic diseases eg: (HTN, DM, cancer) and risk factors eg:(bedridden, postpartum, CCP, central line, idiopathic) had no statistical significance as P value < 0.05

Table 2. Patients' Clinical picture, DVT extension and complications comparison between the two groups

Variables		Group A	Group B	P-value
Hotness	Yes	17 (48.6%)	18 (51.4%)	0.811
	No	18 (51.4%)	17 (48.6%)	
Tenderness	Yes	23 (65.7%)	21 (60%)	0.621
	No	12 (34.3 %)	14 (40%)	
DVT extension	Iliac	13 (37.1%)	16 (45.7%)	0.467
	Femoral	32 (91.4%)	31 (88.6%)	0.69
	Calf	24 (68.6 %)	30 (85.7 %)	0.088
Bleeding	Yes	0 (0%)	4 (11.4 %)	0.039*
	No	35 (100%)	31 (88.6%)	
Recurrence	Yes	1 (2.9%)	2 (5.7%)	0.55
	No	34 (97.1%)	33 (94.3%)	

Regarding the clinical presentation of the patients in the two studied groups, there is no significant statistical difference between two groups. Group A (tenderness 65.7%, hotness 48.6%) Group B (tenderness 60%, hotness 51.4%). Regarding recurrence rate between the two studied groups it was found that there is no significant difference with P-value (0.55). Group A (recurrence 2.9 %), Group B (recurrence 5.7%).While for bleeding. There is significant statistical difference between two studied groups with P-value (0.039) .Group A (bleeding 0%), Group B (bleeding 11.4 %) as P value < 0.05

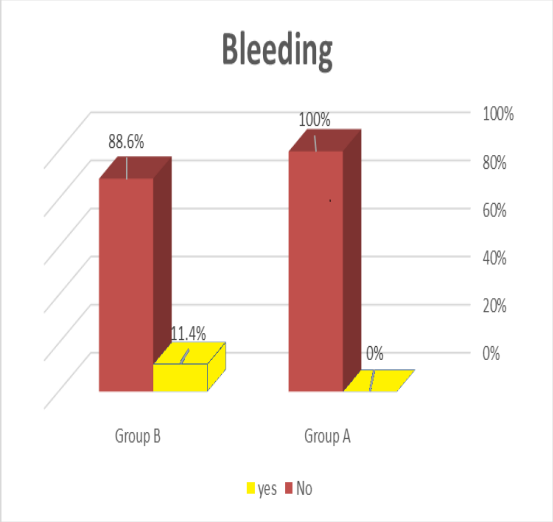

Fig.1. Bleeding comparison between the two groups

Regarding recanalization rate which was followed by regular venous duplex (1.5 month, 3 months and 6 months intervals) it was noticed that there is no significant difference between the two groups with P-value < 0.05

Table 3. Patients' Duplex scans for follow up

Variables		Group A	Group B	P-value
Duplex after 1.5 months	Not recanalized	9 (25.7%)	9 (25.7%)	0.96
	Partial recanalized	15 (42.9%)	16 (45.7%)	
	Recanalized	11 (31.4%)	10 (28.6%)	
Duplex after 3 months	Not recanalized	0 (0%)	1 (2.9 %)	0.57
	Partial recanalized	15 (42.9%)	16 (45.7%)	
	Recanalized	20 (57.1%)	18 (51.4%)	
Duplex after 6 months	Not recanalized	1 (2.9 %)	2 (5.7%)	0.76
	Partial recanalized	3 (8.5%)	4 (11.4%)	
	Recanalized	31 (88.6%)	29 (82.9%)	

Discussion

Deep vein thrombosis and pulmonary embolism are both components of venous thromboembolism, which is referred to simply as VTE. This condition poses a significant risk to public health. Warfarin, a vitamin K antagonist, was the major treatment for venous thromboembolism (VTE) for many years. In recent years, however, the Food and Drug Administration (FDA) has approved several novel oral anticoagulants (NOACs) to treat VTE. **(Schulman et al., 2009)**.

XXWarfarin has slow-acting effects that are unpredictable due to the interactions it can have with meals and other medications, in addition to a metabolism that is highly variable. As a result of its narrow therapeutic window, routine coagulation monitoring in the laboratory and appropriate dosage adjustments are required in order to keep blood coagulation within the targeted therapeutic window.**(Eriksson et al., 2011)**

A novel oral anticoagulant called rivaroxaban works as a reversible and selective factor Xa inhibitor. It can be taken by mouth. In addition to having minimal liver toxicity, it possesses predictable pharmacokinetics and pharmacodynamics, less interaction with foods, drugs, and individual characteristics like age, sex, weight, and ethnicity, and it has fewer interactions with these factors. One of the many advantages of this medication is that it has a more generous therapeutic window than warfarin does. This, in essence, means that the same therapeutic effect can be accomplished in spite of the physiological fluctuations that occur in the blood concentration of the medicine. Because of this, there will be less interference from the outside world in its anticoagulant actions, which should lead to better and faster recanalization of thrombi.**(Galego et al., 2017)**.

We aimed in our study to compare between rivaroxiban and warfarin regarding efficacy, safety and complications in patients with DVT In our study, we could not find a significant statical difference between the two studied groups regarding age, gender, risk factors eg: (bedridd-en, postpartum, major surgery, central lines, cancer and long travels) and chronic diseases eg: (HTN, DM and cardiac patients).

The opposite finding was detected in **Barco et al.(2013)** that more comorbid conditions that require concomitant medication and drug interactions can influence oral anticoagulants efficiency used in VTE management.

Also according to **Llorca et al., 2021** It was found that women are more likely to receive NAOCs than men and that observed difference can not be explained according to clinical factors.

On the contrary, **Hindricks et al. (2021)** found that age is a significant risk factor for stroke and bleeding in patients with thromboembolism who are receiving anticoagulants as the 2020 guidelines of the European Society of Cardiology (ESC) recommend non-vitamin K antagonist oral anticoagulants (NOACs) for the prevention of stroke over vitamin K antagonists (VKAs), and that without age restrictions, NOACs are preferred for stroke prevention.

On the contrary, **Pengo et al. (2005)** found that rivaroxaban does not protect high-risk

patients e.g. (ischemic patients and antiphospholipid S) from arterial events such as ischemic strokes and myocardial infarction.

Regarding recanalization rate, as followed by regular venous duplex (1.5 month, 3 months and 6 months intervals) it was noticed that is no significant difference between the two groups .As in group A patients, complete recanalization was achieved in 88.6% of patients at 6 months duration as confirmed by duplex ultrasonography scan while in group B patients receiving warfarin, recanalization rate was 82.9%.

However, in the J-EINSTEIN-DVT/PE randomised study that was carried out in Japan, patients diagnosed with DVT or PE were given either oral rivaroxaban or VKA for their treatment. After 22 days of treatment, imaging scans demonstrated that normalisation had occurred in 27 percent of the patients who had been administered rivaroxaban and in 15.8 percent of the patients who had been treated with VKA. Examination results showed that at the conclusion of treatment, patients in the rivaroxaban group showed normalisation in 62 percent of cases, whereas patients in the VKA group showed normalisation in 31.6 percent of cases. At the conclusion of the J-EINSTEIN-DVT/PE research, 95.8 percent of patients in the group that was treated with rivaroxaban showed signs of having improved or returned to normal on exams, in comparison to 89.5 percent of patients in the group that was treated with VKA **(Yamada S et al.,2015)**.

Also the opposite finding was detected in **Kuznetsov et al.(2016).** Moreover, in a research of 102 patients with iliofemoral venous thrombosis, there were no incidences of residual thrombotic occlusions of the major veins in patients who were given rivaroxiban. On the other hand, thirteen percent of patients who were given warfarin showed persistent thrombotic occlusion. When comparing the recurrence rate of each of the groups that we researched, we found that there was no discernible difference between them. Group A had a recurrence rate of 2.9 percent, while Group B had a rate of (recurrence 5.7 percent). On the other hand, a retrospective study that was carried out in the Danish national databases and was restricted to patients who had experienced an event of unprovoked VTE indicated that only rivaroxaban was related with a reduction in recurrent VTE in comparison to warfarin. **(Larsen et al.,2017)**.

The difference between our study and J-EINSTEIN-DVT/PE randomized study, **Kuznetsov et al.(2016)** and Larsen TB et al., regarding recanalization rate and recurrence may be due to small sample size in our study. Regarding bleeding, there is significant statistical difference between two studied groups as 4 cases suffered from bleeding receiving warfarin that required dose reduction, tight follow up of INR and clinic visits.

On the contrary according to **Larsen et al.(2017)** it was found there is no significant difference regarding risk of major bleeding between rivaroxiban and warfarin.

Matching with **Piccini et al.(2016**), Rivaroxaban was found to be well tolerated and associated with lower risk of bleeding than warfarin, due to reduced predisposition for drug interactions.

Also in study of **Connolly et al.(2009)** NOACs have been tested as alternatives to warfarin in four randomized trials involving 71 683 patients. The pooled data indicate that NOACs compared with warfarin significantly reduce stroke or systemic embolism by 19%, major bleeding by 14%, fatal bleeding by 51%, and mortality by 10%.In 2012, individuals suffering from VTE who were being treated with oral anticoagulants were given warfarin as their prescription medication. By 2017, the use of warfarin had dropped significantly, and it was only prescribed to 17.5 percent of VTE patients. Patients were advised to take rivaroxaban at a rate of 42.7 percent, apixaban at a rate of 38.6 percent, dabigatran at a rate of 1.3 percent, and edoxaban at a rate of 0.1 percent. Since 2014, when it was prescribed to 40.8% of patients, usage of rivaroxaban has been relatively constant. **(Mueck et al., 2014)**

The new oral anticoagulants, also known as NOACs, are a significant advancement since, in contrast to warfarin, they have a constant dose, a predictable action, and do not require

routine laboratory monitoring. In addition to this, there are less drug and food interactions with these medicines, which ought to lead to an improvement in the patients' overall quality of life. In the treatment of patients who have venous thromboembolism (VTE), major randomised controlled trials (RCTs) of phase III have demonstrated that rivaroxaban has equal efficacy and safety to warfarin **(Okumura et al., 2011;Pokorney et al., 2015)**

Conclusion

Rivaroxiban and Warfarin seem to have same efficacy regarding symptoms relief and prevention of DVT reccurence. Rivaroxiban is better than warfarin regarding bleeding risk, safety in all age groups, compliance and follow up as no need of laboratory monitoring. Every patient with newly discovered DVT takes in consideration Rivaroxiban as first choice regarding its advantages in comparison with Warfarin as there are less bleeding risk, no need of regular lab monitoring, suitable of all age groups and noticed compliance.

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