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Original Article / Özgün Makale

Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis: surveillance of thrombus regression

Uzun dönem derin ven trombozu tedavisinde düşük molekül ağırlıklı heparinlerle oral antikoagülanların karşılaştırılması: Trombus gerilemesinin takibi

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Background: This study aims to compare the effects of low molecular weight heparin (LMWH) versus oral anticoagulants on thrombus regression and post-thrombotic syndrome (PTS) in the treatment of long-term acute deep vein thrombosis (DVT).

Methods: One hundred-forty patients with acute, proximal, unilateral DVT of the lower limbs confirmed by Doppler ultrasonography were enrolled to study to receive a-six-month treatment with LMWH or vitamin K antagonist (VKA). Seventy four patients were divided into two groups except excluded patients and noncompleters. Tinzaparin sodium was administered subcutaneously once daily in a weight-adjusted dose of anti Xa 175 IU/Kg bodyweight in LMWH group, while warfarin was administered 5 mg/day for VKA group. Doppler ultrasonography was used to evaluate thrombus regression, recanalization and venous reflux at intervals of 1, 3, 6 and 12 months. All patients were followed up for 12 months.

Results: Comparing ultrasonographic findings derived from both groups, the gradual reduction over time reflecting thrombus regression was more prominent in the LMWH group. A higher reduction in thrombus size in LMWH group was associated with lesser clinical events of recurrence and consequently a lesser rate of PTS. No cases of major bleeding were experienced in LMWH group, while two cases (5%) were observed in the VKA group.

Conclusion: Unmonitored subcutaneous administration of LMWH at a fixed daily dose was more efficient in achieving recanalization of leg veins and safe, at least as much as oral anticoagulant, after long-term administration. These results suggest that LMWHs, compared to other treatment of choices, may represent a real therapeutic advance in the long-term management of DVT.

Key words: Doppler; low molecular weight heparin; oral anticoagulant; reflux; ultrasonography; venous thromboembolism.

Amaç: Bu çalışmada uzun dönem akut derin ven trombozu (DVT) tedavisinde, düşük molekül ağırlıklı heparin ile oral antikogülanların (DMAH) trombüs gerilemesine ve post-trombotik sendrom (PTS) gelişimine etkileri karşılaştırıldı.

Çalışma planı: Doppler ultrasonografi ile tanı konulmuş, akut, proksimal, tek taraflı alt extremite DVT'si olan 140 hasta, altı aylık DMAH veya vitamin K antagonisti (VKA) ile tedavi edilmek üzere çalışmaya dahil edildi. Çalışma dışı bırakılan ve çalışmayı tamamlayamayan hastalar çıkarıldıktan sonra kalan 74 hasta iki gruba ayrıldı. DMAH grubunda tinzaparin sodyum, kiloya göre 175 IU/kg anti XA şeklinde günde tek doz subkutan, VKA grubunda ise varfarin günde tek doz oral yolla uygulandı. Doppler ultrasonografi kullanılarak 1, 3, 6. ve 12. aylarda yapılan takiplerde trombüs gerilemesi, rekanalizasyon ve venöz yetmezlik değerlendirildi. Tüm hastalar 12 ay boyunca takip edildi.

Bulgular: İki grup arasındaki ultrasonografik bulgular karşılaştırıldığında; DMAH grubundaki trombüs çapı gerilemesinin tüm tedavi süresi boyunca daha belirgin olduğu görüldü. DMAH grubunda trombüs çapındaki gerilemeye paralel olarak, rekürren venöz tromboemboli ve PTS oranlarında daha düşük seyretti. Tedavi süresi boyunca DMAH grubunda herhangi bir majör kanama görülmezken, VKA grubunda iki (%5) hastada majör kanama görüldü.

Sonuç: Çalışmamızda takip edilmeyen günde tek doz subkutan olarak uygulanan DMAH tedavisinin, oral antikoagülan tedaviye kıyasla, bacak damarlarının rekanalizasyonunu elde etmede daha etkin olduğu ve en az oral antikoagülan tedavi kadar güvenli olduğu görüldü. Sonuçlar, uzun dönem DVT tedavisinde DMAH'lerin, diğer tedavi seçeneklerine kıyasla, gerçek bir tedavi üstünlüğü olduğunu göstermektedir.

Anahtar sözcükler: Doppler; düşük molekül ağırlıklı heparin; oral antikoagülan; reflü; ultrasonografi; venöz tromboemboli.

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Deep venous thrombosis (DVT) of the lower extremities is recognized as a cause of both pulmonary embolism (PE) and post-thrombotic syndrome (PTS).[1] The main objectives of anticoagulant therapy in the initial treatment of this disease are to prevent thrombus extension as well as early and late recurrences of venous thromboembolism (VTE).[2] Although standard anticoagulation (heparin followed by oral anticoagulation) is currently considered the standard of care for the prevention of PE and recurrent DVT, it remains ineffective in removing the thrombus burden. Consequently, it does not prevent PTS, which can appear months or even years after the acute episode of DVT.[2,3]

Long-term therapy has two goals: to complete the treatment of the acute episode of DVT and to prevent new episodes of VTE that are not directly related to the acute event. For patients with unprovoked DVT, treatment with a Vitamin K antagonist (VKA) is recommended for at least three months.[3] In addition, the consequences of a new episode of VTE and of a bleeding episode need to be considered.

Even with optimal anticoagulant treatment, acute symptoms of DVT, such as leg pain and swelling, can take weeks to subside, and 20-60% of patients develop chronic PTS, which is characterized by leg pain, heaviness, swelling, and in severe cases, skin ulcers.[4] In the study by Kahn et al.[5] involving 387 patients, the influences of PTS and other characteristics on the quality of life at two years were evaluated, and the cumulative incidence rate of PTS was 47%.

The aim of this study was to evaluate the rate of regression in thrombus size between two unprovoked DVT groups which were given two different medical anticoagulant protocols and then investigate them with regard to the development of PTS.

PATIENTS AND METHODS

Patients

We conducted a prospective, randomized clinical study to compare two groups that had two different medical treatment protocols. The patients who agreed to participate were chosen at random during the study, and written informed consent was obtained from all of them. Our hospital's ethics committee also approved the study protocol. Between January 2008 and November 2011, 140 patients with confirmed, unprovoked DVT were enrolled in this trial. Thirty-four participants were excluded because of pregnancy (n=4), previous DVT (n=13), a history of heparin-induced thrombocytopenia (n=3), previous treatment with unfractionated heparin (UFH) for more than 24 hours (n=10), surgery within the previous five days (n=3), or refusal to give informed consent (n=1).

The patients were randomly assigned into two groups by a consecutive alternating method. Thirty-two of the patients were unable to complete the follow-up due to a variety of reasons; therefore, 74 patients were ultimately included in the study. Thirty-eight were assigned to receive long-term tinzaparin [low-molecular-weight heparin (LMWH) group] and 36 received coumadin (VKA group).

The patients in the two groups were comparable with regard to age, gender, weight, and personal histories, and the various predisposing factors did not vary significantly between the groups (Table 1).

During the study period, 530 Doppler ultrasonography scans (DUS) were performed on the 140 patients over a period of 31 months, with a total of 190 for the LMWH group and 180 for the VKA group. Additionally, DUS was performed only once on the 34 excluded patients for diagnostic reasons. Patient progress throughout this study is shown in a flow chart (Figure 1).

The VKA group had 14 participants who failed to complete the study. Treatment was interrupted for two patients due to thrombosis recurrence, one had major bleeding, and the other 11 dropped out of the study for nonmedical reasons. In the LMWH group, the tinzaparin was withdrawn from a 68-year-old female with iliofemoral thrombosis after 30 days of treatment because of thrombocytopenia. Seventeen other patients quit the study for nonmedical reasons.

Regiments of treatment

In the long-term LMWH group, tinzaparin sodium (Innohep) (Leo Pharmaceutical Products Ltd., Ballerup, Denmark) was administered subcutaneously once a day in a weight-adjusted dose of 175 IU/kg Anti Xa bodyweight for a period of six months. Medical treatment was also begun using conventional popular antithrombotic therapy[2] for one week. During this time, the VKA group was being administered coumadin (Zentiva Eczacıbaşı Corporation Medical Products), and the same antithrombotic therapy was also introduced to this group. Furthermore, we encouraged patients in both groups to use a pair of elastic compression stockings with an ankle pressure gradient of 30 to 40 mmHg.

Doppler scan evaluation

Consecutive symptomatic patients who were objectively documented with lower limb DVT following DUS were considered for entry into this study. For this purpose, the Toshiba Xario SSA-660A series (Toshiba

Table 1. Baseline clinical characteristics of the patients

Characteristics	LMWH group			VKA group		
	n	%	Mean±SD	n	%	Mean±SD
Number of patients	38		36			
Age (years)			51.6±15.3			50.7±13.2
Gender						
Female	20			17		
Male	18			19		
Body mass index (kg/m^2)		25.7			26.3	
Side						
Left	21			20		
Right	17			16		
Deep venous thrombosis level						
Iliofemoral deep venous thrombosis	11			13		
Femoral deep venous thrombosis	9			8		
Femoropopliteal deep venous thrombosis	18			15		
Etiology of deep venous thrombosis						
Idiopathic	19			15		
Recent trauma/surgery	8			7		
Immobilization	5			6		
Malignancy	2			5		
Oral contraceptives	4			3		

LMWH: Low-molecular-weight heparin; VKA: Vitamin K antagonist; SD: Standard deviation.

Medical Systems Corporation, Nasu-Tokyo Japan) color Doppler ultrasound system was used with the 4.8-11 MHz Toshiba PLT 704 AT linear transducer (Toshiba Medical Systems Corporation, Nasu-Tokyo Japan). We examined the deep veins, including the common and external iliac veins, the common femoral vein (CFV), the femoral vein (FV) along the thigh, the popliteal vein (PV), and the infrapopliteal vein.

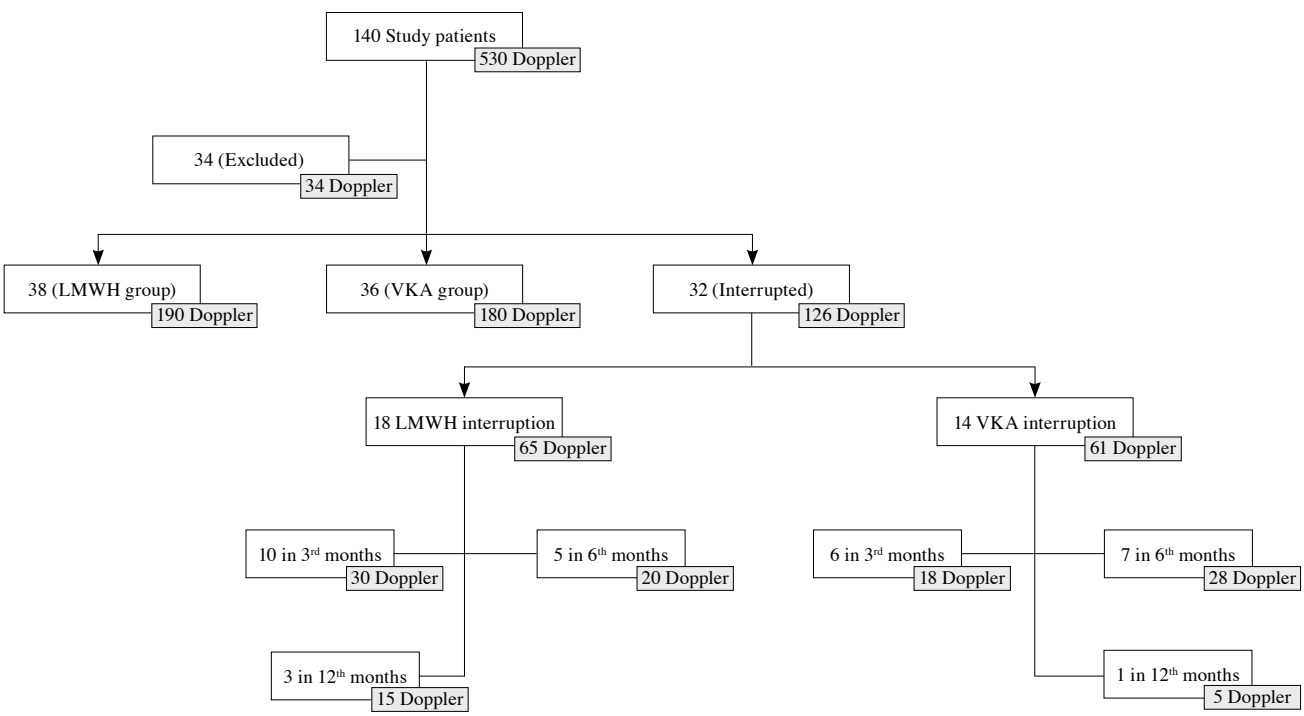

Figure 1. Enrollment scheme. Flow chart of the study. LMWH: Low molecule weight heparin; VKA: Vitamin K antagonist.

The great and small saphenous veins were also examined. In addition, the standard findings of partial or complete venous incompressibility and absent or diminished Doppler flow signals were analyzed. Venous flow augmentation was accomplished by manual compression immediately distal to the venous segment under examination.

For the evaluation of DVT at diagnosis and at the one, three, six, and 12-month follow-up, an objective and reproducible quantitative Doppler scan score[6] was obtained with the addition of degrees of thrombi present in the CFV, the superficial femoral vein (SFV), and the PV with five grades at each segment. The following scoring system was used: four points for complete occlusion (100%), three for severe occlusion (61-99%), two for intermediate occlusion (31-60%), one for slight thrombosis (1-30%), and 0 for patency (0%). The maximum value was 12 points (4x3).

Additionally, at six and 12 months, the Doppler scan follow-up examination included checks on the presence of venous flow and reflux in the deep veins, superficial veins, and perforating veins. Reflux in the deep or superficial venous system was defined as reversed flow with a velocity of more than 10 cm/second or valve closure lasting more than two seconds.[7] The Doppler scan examinations (at diagnosis and follow-up) were interpreted independently without any knowledge of group allocation to prevent bias.

Follow-up

When the patients visited our outpatient clinic for follow-up, they underwent a detailed physical exam. Complete blood count (CBC) and coagulation parameters [activated partial thromboplastin time, prothrombin time and international normalized ratio (INR)] were evaluated at the time of enrollment and during follow-up. At each visit, the patient underwent a clinical evaluation according to a modified Villalta scale[8] and a Doppler ultrasonography assessment of the affected lower limb. They were then scored according to the presence of five leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six objective signs (pretibial edema, skin induration, hyperpigmentation, new venous ectasia, redness, and pain during calf compression). The signs and symptoms were rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). The clinical evaluation outcomes were classified as follows: patients with a total score of greater than 14 points or with a venous ulcer were defined as having severe PTS; those scoring between five and 14 points were categorized as having mild PTS, and those with less than five points were identified as having no PTS.

The primary endpoints were the recanalization of the vein segment as expressed by the reduction in the size of the thrombus bulk and the development of reflux in the affected veins during the study period.

The secondary endpoints were the development of objectively documented recurrent VTE (recurrent DVT and PE) along with major and minor hemorrhagic complication incidence rates and mortality throughout the study period. The overall incidence rates of major events were also considered.

Statistical analysis

Statistical analysis was performed with Graphpad Instat software (GraphPad Software Inc., San Diego, California, USA) version 3 for Mac and the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 11.5 for Windows. All values were expressed as mean ± standard deviation (SD). Comparisons of the variables between the two study groups was performed using the Mann-Whitney U test while comparisons of the variables within the groups was made using the Friedman test and Dunn's multiple comparison test as a post-test. A p value of <0.05 was considered statistically significant.

RESULTS

Thrombus regression

When comparing the ultrasonography scores derived from the two study groups, the gradual reduction over time that reflects thrombus regression had more prominent results in the LMWH group (Figure 2). Thrombus lysis appeared earlier and more extensively by LMWH than by VKA (Table 2).

Three venous segments were routinely explored in each limb, and the segmental scores were added to obtain the global scores. The initial mean clot size score was similar in both groups, and this decreased during follow-up in all DVT locations. We found that the quantitative Doppler scan score showed statistically significant improvement between the LMWH group and the VKA group after iliofemoral and femoropopliteal DVT for every checkpoint interval and at the first and third month in popliteal DVT (Figure 3a-c). The mean thrombus size decreased after tinzaparin treatment in the popliteal thrombus at the sixth and 12th months, but no statistical significance was found with respect to the VKA (Figure 3c).

When we focused on the body and tail segments of the thrombus bulk during the DUS follow-up period, regression peaked in the third month ($p<0.001$) and continued until the 12th month. When the level of regression was compared in the first three months and

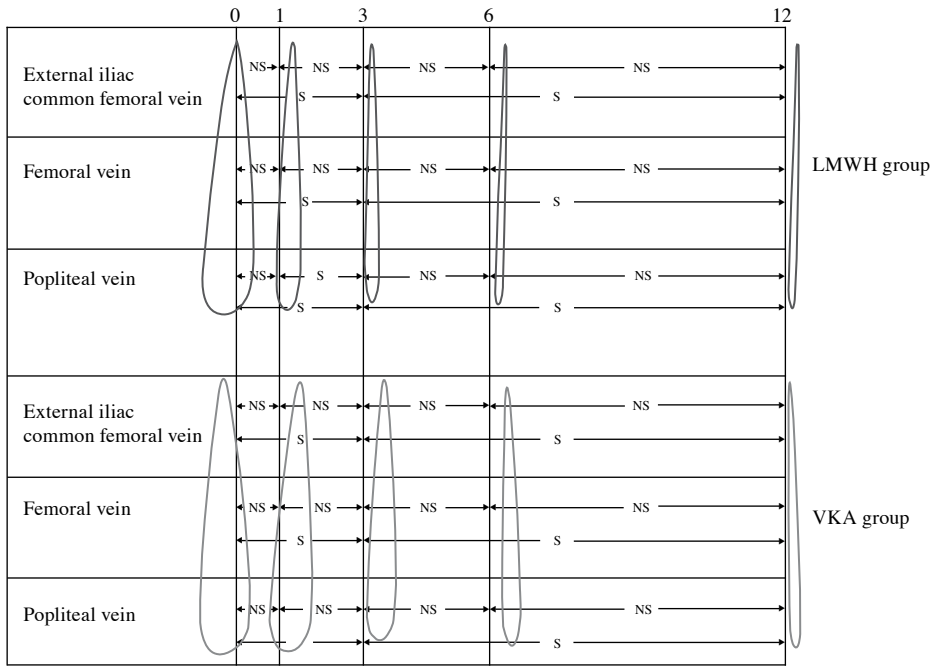

Figure 2. Thrombus regression scheme. The two groups were compared for thrombus regression at the one, three, six, and twelve-month follow-ups. Thrombus bulk sizes were measured with B-mode ultrasound imaging. In this illustration, the thrombus regression rate comparisons are shown as either being statistically non-significant or significant between the outpatient visits. The thrombus regressions are modeled. NS: Non-significant; S: Significant; LMWH: Low-molecular-weight heparin; VKA: Vitamin K antagonist.

in the second late-treatment period between the third and 12th months, there were more favorable results in the first period ($p<0.0001$). Regression of the thrombus head, located caudally in the popliteal vein, was at peak level and proceeded constantly, and head regression was faster compared with the body and tail segments ($p<0.001$) (Figure 2).

Laboratory findings

There were no significant alterations in the blood count throughout the study. Nevertheless, one member of the LMWH group with iliofemoral DVT exited the study due to heparin-induced thrombocytopenia (HIT) (platelet count 70.000/mm^3).

Venous thromboembolic recurrences

There were three episodes of symptomatic recurrent VTE in three patients (8.3%) in the VKA group, and the reason for these recurrences was thrombosis involving a previously affected extremity. In contrast, no recurrence occurred in the LMWH group. Despite thoracic pain episodes appearing in some patients (n=3), we could not verify them as having PE through CT.

Table 2. Thrombus regression during the study period

	Preoperative treatment	1st month	3rd month	6th month	12th month
LMWH group					
Common femoral	1.98±0.21	1.21±0.17	0.62±0.1	0.38±0.06	0.25±0.06
Femoral	2.25±0.23	1.43±0.17	0.94±0.10	0.58±0.07	0.38±0.05
Popliteal	2.6±0.2	1.34±0.17	0.74±0.13	0.43±0.07	0.29±0.06
VKA group					
Common femoral	2.01±0.15	1.42±0.15	1.0±0.11	0.78±0.13	0.62±0.1
Femoral	2.4±0.17	1.95±0.21	1.54±0.19	1.14±0.17	0.89±0.12
Popliteal	2.85±0.24	2.31±0.20	1.71±0.19	1.12±0.20	0.77±0.12

LMWH: Low-molecular-weight heparin; VKA: Vitamin K antagonist; The table shows thrombus regression (mean±SD) over a period of approximately 12 months. The data was obtained using Doppler ultrasound measurements and is presented in centimeters.

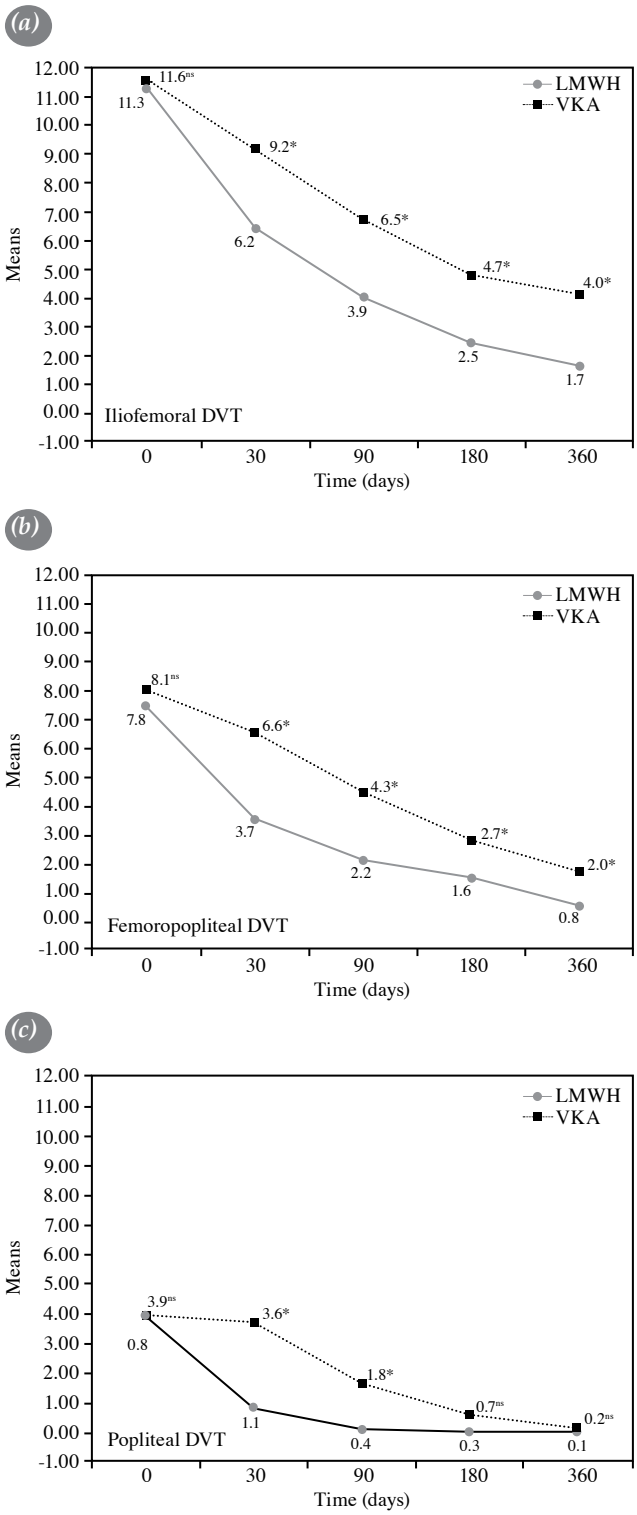

Figure 3. Thrombus regression graphic. The effects of both treatments on the evaluation of thrombosis as expressed by a quantitative Doppler scan score according to the DVT level. **(a)** Iliofemoral venous segment. **(b)** Femoropopliteal venous segment. **(c)** Popliteal venous segment. DVT: Deep venous thrombosis; LMWH: Low-molecular-weight heparin; VKA: Vitamin K antagonist; NS: Non significant; * Statistically significant.

Complications

There were no deaths reported due to bleeding, but life-threatening gastrointestinal hemorrhage occurred in two cancer patients who received VKA (5.5%). There were four cases (11.1%) of minor bleeding (ecchymosis or epistaxis) in the VKA group versus one (2.6%) in the LMWH group.

Evaluation of venous reflux

The affected limbs were examined for the presence of superficial, perforating, and deep venous reflux and for the development of valve incompetence as part of the routine ultrasound scanning conducted at the one, three, six, and 12-month follow-ups.

Reflux was significantly less frequent in the deep venous system (13.1% versus 25.0%) and in the perforating veins (17.9% versus 32.2%) after LMWH treatment. Reflux rates in the superficial (15.7% versus 22.2%) venous system showed no significant differences between the two groups (Table 3).

Post-thrombotic syndrome

Six of the 38 limbs (15.7%) developed mild PTS in the LMWH group, and the main symptoms for these patients were pain, heaviness, and edema of the affected limbs after activity. Mild pruritus was also present in eight limbs, but none of these had severe PTS. However, in the VKA group, 15 of the 36 limbs (41.6%) developed mild PTS, and these patients primarily suffered from pretibial edema, cramps, and heaviness of the affected limbs. Furthermore, four of these limbs (11.1%) had severe PTS. The median total PTS score was four (range: 0-9) in the LMWH group and nine (range: 4-13) in the VKA group.

DISCUSSION

Post-thrombotic syndrome is one of the most serious long-term complications of DVT in the lower limbs, and it affects 23–60% of patients following an episode of DVT.[9] Furthermore, patients with a history of DVT have a 26 times greater risk of venous insufficiency when compared with those having no prior history.[10] The fundamental pathophysiological disturbance found in these patients is sustained venous hypertension resulting from valvular incompetence, outflow obstruction, calf muscle dysfunction, or some combination of the three.[11] The hemodynamic severity of chronic obstruction is complex and differs markedly depending on the level and extent of the affected venous segments,[12] the degree of collateralization, and any recanalization that may occur. The pharmacological lysis of a thrombus located in the deep venous system is an attractive therapeutic

Table 3. Total vein reflux measured with Doppler ultrasonography scans 12 months after the first episode of deep venous thrombosis

Level	Deep venous system				Superficial venous system				Perforating veins			
	LMWH*		VKA		LMWH		VKA		LMWH*		VKA	
	n	%	n	%	n	%	n	%	n	%	n	%
Iliofemoral	3		5		3		6		3		4	
Femoral	1		2		1		2		1		2	
Popliteal	1		1		0		0		1		2	
Infrapopliteal	0		1		1		0		2		3	
Total	5	13.1	9	25	6	15.7	8	22	7	18.4	11	30.5

LMWH: Low-molecular-weight heparin group; VKA: Vitamin K antagonist group; The numbers of the final venous reflux are shown. The insufficiencies in the deep and perforating veins were more significant ($p<0.05$) in the VKA group after 12 months of treatment (*).

option because removal of this mass could prevent PTS if lysis occurs before the valves are destroyed.[13]

The short-term outcome of the initial anticoagulant therapy for patients with acute DVT has been studied extensively, and it has been demonstrated that LMWH treatment is at least as effective and safe for the initial treatment as unfractioned heparin and warfarin.[14] However, the long-term clinical course of this treatment and its impact on PTS has not been investigated as thoroughly.

Some disadvantages exist with VKA. In addition, oral anticoagulant therapy in elderly patients presents further problems.[15] Therefore, before initiating oral anticoagulant treatment in elderly patients, the risk/benefit ratio of the treatment must be considered. If they are placed on oral anticoagulant therapy, careful attention must be paid to the INR.[16]

On the other hand, LMWH treatment, which was used empirically for many years as an alternative to UFH for long-term secondary VTE prophylaxis under specific conditions, such as an increased risk of hemorrhage, complications from previous VKA use, pregnancy and other contraindications for VKA, and the inability or unwillingness to have regular laboratory monitoring or take oral medication, is now a part of everyday clinical practice. Our study focused on the evaluation of LMWH that was administered over a six-month period as a replacement for VKA in different patient populations.

Daskalopoulos et al.[17] published the first open-label, prospective, randomized clinical study associated with the use of tinzaparin. The results of this study were confirmed by a more recent larger study by the longitudinal investigation of thromboembolism etiology (LITE) trial investigators in which two articles were published that studied the advantages and disadvantages of self-managed long-term tinzaparin therapy for DVT[18] and the effectiveness of LMWH in a subgroup of cancer patients with acute proximal DVT.[19]

These studies agreed that tinzaparin is a safe and effective alternative to the ''usual care''. However, some differences came forth from those studies that merit mentioning. For example, the LMWH treatment was administered for three months in almost all of those studies[18,19] but for six months in our study. We considered this length of time to be more appropriate for treating proximal thrombosis, especially in patients with comorbidities predisposed to VTE and its recurrence.

Both therapeutic regimens have been proven to be effective in preventing the progression of the thrombus and for allowing the recanalization of affected veins. When comparing the ultrasonography scores derived from the two study groups, the findings suggest that tinzaparin performs better than long-term warfarin in the resolution of thrombosis. As an interpretation, we can conclude that in the LMWH group, thrombus shrinkage in response to the treatment is faster and reaches its peak in all venous segments in a short period of time (Figure 3). This suggests that this medical regimen should be continued for at least three months.

The positive effects of VKA continue for 12 months, but they are weaker overall than for LMWH. The reason for the efficiency of LMWH regarding the regression of the size of the thrombus versus what is achieved with VKA may be associated with favorable characteristics, such as a bioavailability of greater than 95% after subcutaneous administration, a longer half-life, the activity being dose-independent, and low binding to plasma proteins and to proteins released from activated platelets and endothelial cells.[20] All of these make it possible to maintain more stable levels of anticoagulation, which is not always possible with VKA, despite the performance of frequent laboratory controls.

In previous studies with sequential Doppler scan examinations of patients with DVT treated with VKA, it was confirmed that the clearance of a thrombus was a gradual process and that recanalization in previously occluded venous segments occurred over different periods.[21] We found that earlier recanalization induced by tinzaparin resulted in less valve incompetence. Prandoni and Kahn[22] concluded that a lack of recanalization within the first six months after a thrombotic episode is an important predictor of PTS.

In addition, the latest systematic review of the literature by the Cochrane Collaboration concludes that LMWH treatment is significantly safer than VKA.[23] As further proof of the safety of treatment with LMWH, our data showed no differences between the LMWH and VKA groups regarding bleeding, HIT, or mortality.

A higher recurrence rate among patients with limited thrombus regression could justify a prolonged prophylactic therapy. The absence of normalization in the use of DUS after the first episode of DVT appears to be a factor that promotes recurrence.[24] In our study, after a 12-month follow-up, none of the 38 patients who received LMWH and three (8%) of the 36 patients who received VKA experienced a recurrence of venous thrombosis.

Taking into account all of our data and the current data available in the literature, we conclude that thrombus size evolution is an important predictor of PTS. In our patients who had poor recanalization, there is a greater risk for recurrent VTE and PTS in upcoming years, and this risk is evident in spite of the intense treatment they received. More rapid recanalization with tinzaparin is associated with less recurrence of VTE and less expectation of PTS compared with the use of VKA. The significantly lower superficial and perforating vein reflux rates in the LMWH group were probably a result of very early recanalization and its protective affect on valve function.

In conclusion, we believe that tinzaparin is an effective and safe LMWH that should be considered as an alternative therapeutic treatment for patients with acute proximal DVT.

Declaration of conflicting interests

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