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Experience of a 40-day (6 week) LMWH treatment for isolated distal deep vein thrombosis

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Abstract
Clinical significance of distal deep vein thrombosis (DVT) is important as it can potentially result in pulmonary embolism (PE), DVT extension, DVT recurrence and post-thrombotic syndrome (PTS). Controversy remains about the necessity and modalities of anticoagulation in all distal DVT. Evaluation of the efficiency of a 40-day weight-based low molecular weight heparin (LMWH) treatment in a cohort of 119 consecutive patients with distal DVT. Compression ultrasonography of the lower limb was performed initially for diagnosis as well as at the end of the treatment to identify persistence or resolution of the blood clot. A 3-month follow-up estimated the rates of PE, DVT recurrence, DVT extension, PTS and bleeding. Risk factors for DVT were considered to evaluate a possible correlation between them and the outcomes. In 71.4% of the patients the blood clot was totally dissolved and thrombus persistence was statistically associated with the number of initially involved veins. DVT recurrence occurred in 5% of patients and was also associated with the number of initial clotted veins. DVT extension and PTS rates were present in 1.7% and 3.4% respectively and no patient was diagnosed with PE or bleeding. This retrospective study including a limited number of patients and no control group supports that a 40-day weight-based LMWH treatment after distal DVT seems to be efficient when one single vein is initially affected whereas for multiple vein distal DVT and to avoid potential DVT recurrence, longer than 6 weeks of anticoagulant treatment is required. Our results support safety of the treatment, its potential to prevent DVT extension and the occurrence of PE.

Keywords Distal DVT · LMWH · Multiple vein distal DVT

Highlights

- Controversy exists about distal DVT management (diagnosis and treatment)
- Balance between risks of complications and bleeding is necessary
- This retrospective study supports evidence for safety of a 40-day (6 week) LMWH treatment for single vein distal DVT
- It seems that for multiple vein distal DVT, longer than 6 weeks of anticoagulant treatment is required
- Further studies on high-risk patients with multiple vein distal DVT are needed

Introduction

Deep vein thrombosis (DVT) of the lower limbs may occur in proximal or distal veins that drain muscles and deep tissues. Proximal DVT involves the femoral, iliac, and popliteal veins. Distal DVT affects the infra-popliteal network involving axial (tibial anterior, tibial posterior, peroneal) and muscle (gastrocnemius, soleus) veins. The clinical significance of distal DVT is important because it can potentially result in pulmonary embolism [1] (PE), DVT recurrence, DVT extension and post-thrombotic syndrome [2, 3] (PTS).

Guidelines for management of proximal DVT are well established and most studies recommend a minimum of three months of anticoagulation [4]. Controversy remains though about distal DVT management (diagnosis and treatment), due to the high degree of uncertainty about its

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clinical importance and associated risks. In 2008, the Consensus Conference of American College of Chest Physicians (CCACCP) recommended a 3-month anticoagulant treatment period and follow-up for all diagnosed DVTs [5]. Later on, in 2012, the CCACCP revised that recommendation to serial imaging venous compression ultrasonography (CUS) for two weeks in acute distal DVT in patients without risk factors or severe symptoms [6]. In cases of high-risk patients such as those with positive D-dimer, extensive thrombosis, DVT location close to the proximal veins with severe risk factors (≥ 5 cm in length, > 7 mm in diameter, involving multiple veins), active cancer, history of venous thromboembolism (VTE), unprovoked DVT or inpatients, using the same protocol as for proximal DVT is suggested. In contrast, The National Clinical Guideline published in the same year (2012), focused mostly on the treatment of proximal DVT characterizing distal DVT as less likely clinically important [7]. The following year (2013), during the International Consensus on Prevention and Treatment of Venous Thromboembolism it was recommended that all patients with symptomatic calf DVT should be treated with oral anticoagulants for three months [8]. Finally in 2016, ACCP guidelines for management of distal DVT were in fact identical to those from 2012 [9].

The primary aim of our study was to evaluate the efficacy of a 40-day weight-based low-molecular-weight-heparin (LMWH) treatment in isolated distal DVT. The secondary aim was to estimate the rates of PE, DVT recurrence, DVT extension, and PTS at a 3-month follow-up. Potential risk factors (cf. subjects and methods) that could be related to clot resolution or persistence were also analyzed.

Subjects and methods

We reviewed more than 70 recent articles and reviews on distal DVT treatment efficacies. As depicted above, it is obvious that controversies still exist with respect to distal DVT management according to recent literature. In our hospital, *Cliniques Universitaires St-Luc, Brussels, Belgium*, all DVT are systematically diagnosed (by CUS) and treated with anticoagulants. For proximal DVT, Vitamin K antagonists (VKA), LMWH or direct oral anticoagulants (DOAC) are administered for 3 to 6 months. Since 2010 and for all distal DVT, the protocol that we use is a 6-week (40 days) LMWH treatment. Depending on the outcomes after 40 days, treatment is extended up to 3 months. This protocol was based on the existing literature at the time of the study. Since DOACs are not reimbursable for distal DVT in Belgium, those drugs are not administrated. VKAs were deliberately avoided considering that for many patients, stable anticoagulation would have been reached after many days which would have been incompatible with the hypothesis that 40 days of stable full anticoagulation is sufficient to manage most patients with distal DVTs. In case of contra-indications to LMWH such as allergy or renal dysfunction, patients receive instead VKA but not included in the study. Treatment was started at hospital after initial diagnosis (Day 1) and all patients received standard education on how to follow the treatment. In our practice, patients with DVTs are well informed about the possible consequences of inappropriate treatment and report high compliance. In addition, the short duration of the treatment in our study also encouraged patients to be fully adherent. The records of 124 patients, who were admitted to the *Cliniques Universitaires St Luc, Brussels, Belgium* with a diagnosis of distal DVT within a period of six years, from 2010 to mid 2016, were retrospectively analyzed. Records were identified by searching all patients referred to the hemostasis unit with a diagnosis of DVT. Among 353 patients, 124 were diagnosed with a distal DVT (35.1%) and 229 with a proximal DVT (64,9%). DVT was confirmed by CUS performed at the medical imaging department. All patients were seen by one of the two Hematology consultants, who took a full medical history including all risk factors for DVT, performed clinical examination and prescribed anticoagulation treatment with a scheduled 3-month-follow-up. Only patients who (a) were administered weight-based (1.5 mg/kg/day) LMWH (Enoxaparine-Clexane®) for a 40-day period in the absence of contra-indications (renal dysfunction, allergy to LMWH) after distal DVT diagnosis and subsequently (b) underwent CUS to verify the clot status (complete vein recanalization or clot persistence) at the end of the 40-day treatment period and (c) completed a 3-month clinical follow-up for possible DVT recurrence, DVT extension, PE and PTS, were eligible for the study. Patients with concomitant initially proximal DVT or PE were excluded from the study, whereas patients with concomitant superficial vein thrombosis (SVT) were included. Five patients with distal DVT were excluded from the study (four patients with contra-indications to LMWH and one lost from follow-up) (Fig. 1). No data were collected about those patients' outcomes. DVT extension was defined as persistence of the blood clot after 40 days of

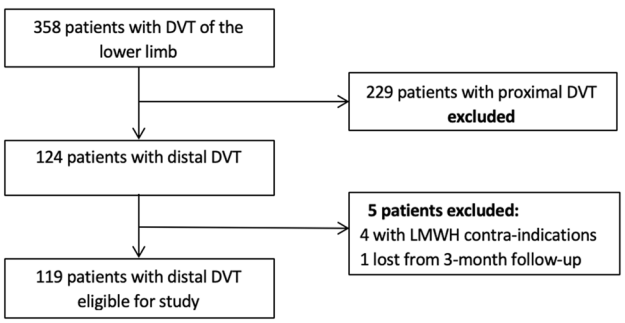

Fig. 1 Patient flow diagram

LMWH treatment and propagation into other proximal or distal veins. PTS was designated as a clinical complication during the 3-month follow-up period with symptoms such as pain, swelling, heaviness, varicose veins cramps at the involved calf based on the Vilalta scale for the diagnosis (score > 4) [10]. Finally, DVT recurrence was defined as a complete clot resolution after 40 days of LMWH treatment and reoccurrence during the 3-month follow-up period. The protocol of the current study was approved by the hospital's ethics committee. Different parameters from the records of these patients were selected for analysis, including: gender, age and weight, the number and name of the affected veins per patient, the presence or absence of SVT at the time of the DVT diagnosis, the CUS results at the end of the 40-day LMWH treatment, DVT recurrence, DVT extension, PE or the presence of PTS within the 3-month follow-up period. Data from the medical and family history of these patients were also examined, namely: previous DVT, cancer status, history of immobility, smoking habits, birth-control pill administration for women, diabetes, cardiovascular risk factors (hyperlipidemia, hypertension), family history of thrombosis, genetic factors such as resistance to protein C, the detection of factor V Leiden activated protein C-resistance (APCR) and prothrombin (FII) mutations, antithrombin deficiency and elevated FVIII were also taken in consideration.

Statistical analysis

The baseline characteristics of patients were summarized as mean and standard deviation (SD) for continuous data and as absolute (n) and relative (%) frequency for categorical variables. All data are presented in 2 × 2 contingency tables where possible. The two-tailed Fisher's exact test was performed in order to evaluate possible differences in the various clinical and pathological features between male and female patients in addition to the frequency of distribution in cases with: dissolved and non-dissolved DVT clots after the period of LMWH administration, DVT recurrence and no DVT recurrence within the 3-month follow-up after period, as well as DVT extension and no extension (only for cases with non-dissolved clots). The Mantel–Haenszel method was applied for the calculation of odds ratios (ORs) and their respective 95% confidence intervals (CIs) in all of the 2 × 2 contingency tables. The two-tailed Fisher's exact test was more favorable in the present analysis compared to the chi squared test, since for many comparisons > 20% of the expected counts in 2 × 2 contingency tables were < 5 and some individual expected counts were < 1 [11]. Comparisons concerning the age and weight of patients were based on the Student's t test. Statistical analyses were performed using the SPSS® software application (version 21.0; IBM® SPSS Statistics, Chicago, IL, U.S.A.) with $P < 0.05$ as the threshold of significance.

Results

Baseline and diagnosis characteristics

The study sample of 119 patients with distal DVT consisted of 33 men and 86 women (27.7% and 72.3% respectively). The frequency distribution of baseline and diagnostic characteristics is shown in Table 1 according to gender. The mean age of men (54.2 ± 14.4 years) was significantly higher than that of women (44.0 ± 17.3 years) ($P = 0.003$). Similarly, weight differences between men and women are noted. The mean weight for men was 84.1 ± 15.5 kg compared to only 68.5 ± 13.0 kg of women ($P < 0.001$). However, body mass index (BMI) was not available. No differences were noted concerning diagnosis characteristics e.g. the type of thrombosis and the number of affected veins between the two genders.

Medical record data

Between the two genders, differences were noted concerning the birth control pill intake, since these pills are only administered in women ($P < 0.001$). More than half of women (59.3%) made use of oral birth control pills (missing data for one woman). Furthermore, men with DVT were found to have 2.73 times more often positive history of recent immobility, compared to women, and this finding was statistically significant ($P = 0.022$, OR 2.730, 95% CI 1.206–6.172).

Treatment and 3-month follow-up outcomes

In 13 out of 33 men (39.4%) and in 21 out of 86 women (24.4%) the clot was not dissolved at the end of the 40-day LMWH administration period, as it is shown in Table 2. This finding was not statistically significantly different between the two genders, ($P = 0.118$). In the majority of patients, namely 85 out of 119 patients (71.4%) clot resolution was observed and was associated with the number of affected deep veins, as shown in Fig. 2. Patients with more than one affected deep veins at initial CUS were at 4.051 times higher risk for presenting a non-dissolved clot after the 40-day LMWH administration period, compared to patients with only one affected deep vein ($P = 0.023$, OR 4.051, 95% CI 1.334–12.285). In fact, 8 out of 34 patients (23.5%) with non-dissolved clot (Group A) had more than one affected deep veins, compared to only 6 out of 85 patients (11.8%) with dissolved clot (Group B). All parameters under study for the 3-month follow-up were not found to differ between the two genders. DVT recurrence was apparent in only 6 (5.0%) patients compared to 113 (95.0%) patients with an uneventful follow-up and was also associated with

Table 1 Baseline and diagnosis characteristics of the study sample according to gender

	Male	Female	P	OR (95% CI)	Whole sample
Sample characteristics					
Number of patients (n)	33 (27.7%)	86 (72.3%)			119 (100%)
Age (years)					
Mean (± SD)	54.2 (± 14.4)	44.0 (± 17.3)	0.003[a]		46.8
Range	27–84	17–89			17–89
Weight (Kg)					
Mean (± SD)	84.1 (± 15.5)	68.5 (± 13.0)	< 0.001[a]		72.8
Range	60–128	46–100			46–128
Diagnosis characteristics					
Type of thrombosis					
DVT + SVT	2 (6.1%)	3 (3.5%)	0.616[b]	1.785 (0.341–9.435)	5 (4.2%)
DVT	31 (93.9%)	83 (96.5%)			115 (95.8%)
Number of deep veins affected					
One	29 (87.9%)	76 (88.4%)	1.000[b]		105 (88.2%)
Two	3 (9.1%)	8 (9.3%)			11 (9.2%)
Three	1 (3.0%)	2 (2.3%)			3 (2.5%)
More than one	4 (12.1%)	10 (11.6%)	1.000[b]	1.048 (0.323–3.443)	14 (11.8%)
One	29 (87.9%)	76 (88.4%)			105 (88.2%)
Affected veins					
Soleus	14 (42.4%)	35 (40.7%)	0.321[b]		49 (41.2%)
Gastrocnemius	4 (12.1%)	11 (12.8%)			15 (12.6%)
Peroneal	15 (45.5%)	28 (32.6%)			43 (36.1%)
Tibial posterior	3 (9.1%)	21 (24.4%)			24 (20.2%)
Tibial anterior	2 (6.1%)	3 (3.5%)			5 (4.2%)
External saphene[c]	2 (6.1%)	3 (3.5%)			5 (4.2%)

[a]Student's t test

[b]Two tailed Fisher's exact test

[c]Superficial vein (excluded from the analysis)

Table 2 Treatment and 3-month follow-up outcomes of the study sample according to gender

	Male	Female	P[a]	OR (95% CI)	Whole sample
Treatment outcome					
CUS characteristics					
Clot not dissolved	13 (39.4%)	21 (24.4%)	0.118	2.012 (0.866–4.685)	34 (28.6%)
Clot dissolved	20 (60.6%)	65 (75.6%)			85 (71.4%)
3-month follow-up outcome					
DVT extension					
Yes	1 (3%)	1 (1.2%)	0.479	2.656 (0.269–26.193)	2 (1.7%)
No	32 (97%)	85 (98.8%)			117 (98.3%)
DVT recurrence					
Yes	2 (6.1%)	4 (4.7%)	0.669	1.323 (0.270–6.559)	6 (5%)
No	31 (93.9%)	82 (95.3%)			113 (95%)
Post Thrombotic Syndrom (PTS)					
Yes	1 (3%)	3 (3.5%)	1.000	0.865 (0.120–6.344)	4 (3.4%)
No	32 (97%)	83 (96.5%)			115 (96.6%)

[a]Two tailed Fisher's exact test

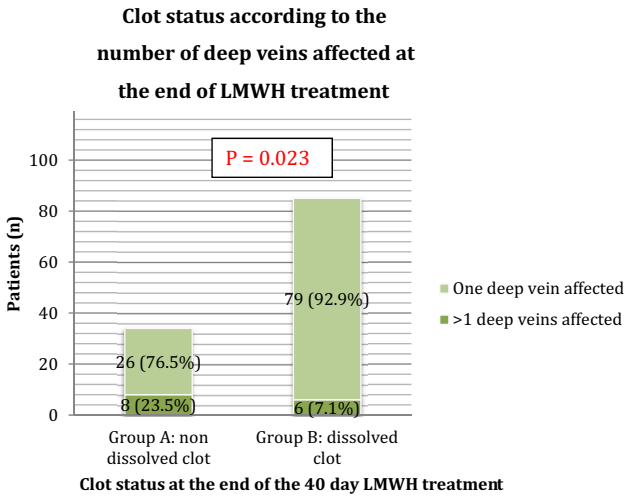

Fig. 2 Distribution of patients according to clot status at the end of the 40-day LMWH treatment

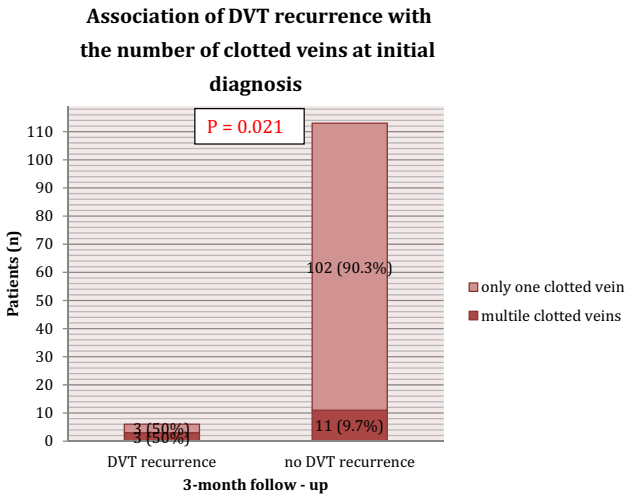

Fig. 3 Distribution of patients according to DVT recurrence within the 3-month follow-up and the number of initially clotted veins

patients who had more than one clotted vein at the time of the diagnosis (Fig. 3). Moreover, patients with more than one affected vein, based on the initial CUS, were at 9.3 times higher risk for presenting DVT recurrence within the 3-month follow-up, compared to patients with only one affected vein (P = 0.021, OR 9.273, 95% CI 1.894–45.818).

Comparison of all characteristics of patients with non-dissolved clot, according to DVT extension after the 40 days of LMWH administration period

All data was summarized according to DVT extension for patients whose clot was not dissolved at the end of the 40-day LMWH administration. Among 34 patients with non-dissolved deep vein clots, DVT propagated in two (5.9%) cases including a man and a woman who were asymptomatic. The peroneal vein was implicated in both of these patients and it was the only affected vein. None of the other parameters under study were also associated with the presence of DVT extension.

Comparison of patient parameters, according to PTS presence, during the 3-month follow-up period

All parameters under study were analyzed according to PTS presence within the 3-month follow-up period. Only 4 (3.4%) out of 119 patients developed PTS symptoms. No association was noted with any parameter under study, including sample characteristics, diagnosis characteristics, treatment outcomes, 3-month follow-up data, as well as medical record data with the presence of PTS.

Pulmonary embolism and bleeding rates

No case of PE was found during the 3-month follow-up period of the 119 patients diagnosed and treated for a distal DVT. Similarly, no case of bleeding or fatal bleeding complication was found during the 40 days of LMWH administration period.

Discussion

Treatment of all isolated distal DVT has been debated and no international guidelines are available, contrary to proximal DVT where treatment guidelines are already established. Debate exists between clinicians who treat systematically distal DVT and others who prefer surveillance by serial CUS. Between accomplished randomized studies, results seem discordant, half of them suggesting the first and half the second option. Up to now, in our hospital *Cliniques Universitaires St Luc*, distal DVT is systematically screened and treated by anticoagulants.

According to our study, women seem to develop distal DVT (provoked or unprovoked) at a younger age than men. On the opposite, Barco et al. demonstrated that women have a higher probability of presenting unprovoked distal DVT as compared to men, but men seem to develop provoked distal DVT in a younger age (18–40 years) than women (55–75 years) [12]. In a study published in 2009 by Galanaud et al., no reference was made to gender as a risk factor for distal DVT [13]. The risk of finding a recent immobility history in our study, such as surgery or cast in the patient's history was about 2.73 times higher in male subjects.

After 40 days of LMWH treatment, the thrombus was dissolved in the majority of the patients. Clot persistence

was statistically associated with multiple vein thrombosis. It seems that a 40-day LMWH treatment is not sufficient when more than one vein is involved. These results are similar to findings by Ferrara et al. who suggested a 6-week anticoagulant treatment for single vein DVT versus 12 weeks for multiple vein DVT [14].

Similarly, DVT recurrence rate in our study was up to 5% (six patients) and also associated with multiple vein thrombosis. Patients with more than one involved vein were at significantly higher risk of recurrence at the 3-month follow-up. Galanaud et al. studied risk factors that may influence recurrence after distal DVT and concluded that such risk factors are the number of thrombosed veins, unprovoked distal DVT and age > 50 years [15]. A more recent study in 2017 by Donadini et al. concluded that the long-term risk of recurrent VTE after distal DVT treated for 4 to 6 weeks is not negligible, particularly in patients with unprovoked distal DVT or cancer [16]. This implies that patients must be divided into different groups in order to receive the adequate treatment period. Finally, a meta-analysis published the same year by Franco et al. confirmed that anticoagulation of distal DVT reduces the rate of recurrent VTE and the incidence of pulmonary embolism compared to no anticoagulation, without increasing the risk of major bleeding [17]. According to this study, a treatment for longer than 6 weeks is preferable over shorter durations. The above-mentioned studies in conjunction with our results could lead us to support that distal DVT involving multiple veins requires longer than 40 days of anticoagulant treatment in order to ensure clot resolution and to avoid potential DVT recurrence. Treatment seems to us necessary due to higher risk of recurrence, but further studies are required to estimate the optimal treatment duration.

DVT extension rates under anticoagulant treatment according to our study were quite low up to 1.7% (two patients) and not statistically associated with any of the patient's characteristic. Taking into account that proximal DVT demonstrates a high risk of resulting in pulmonary embolism [18], no anticoagulation treatment seems unacceptable to us, and it is necessary to prevent the risk of proximal propagation. In contrast to our results are the findings of the CACTUS trial (2016), a randomized double-blind placebo controlled trial comparing 6-week anticoagulation versus no anticoagulation in distal DVT, in which no significant difference in the risk of proximal extension or VTE events was found [19]. However, the CACTUS trial was limited to low-risk patients (without active cancer or previous VTE), whereas our study which was not selective, included several patient categories. In addition, the evidence level of an RCT is indeed superior to that of a retrospective study. Of our cohort, 3.4% of patients developed PTS during the 3-month follow-up period after LMWH treatment. Kearon et al. published a study in 2012 in which recurrent DVT episodes were shown to be a significant risk factor for the development of PTS, and prevention of these episodes was highly recommended [6].

PE rates in the 3-month follow-up period was totally absent in the current study. Indeed, PE is clinically important and may be fatal. Three other studies in which patients did not receive anticoagulation therapy after a distal DVT presented PE rates between 0% and 1.6% within a 3 month-follow up period [20–22].

In addition, our 40-day LMWH anticoagulant treatment didn't provoke bleeding as rates were also 0%. This result in not consistent with the CACTUS trial outcomes (in which anticoagulant treatment increased the risk of bleeding) as mentioned in the recent review article of H. Robert-Ebadi and M. Righini [23].

Our patient-centered approach is in agreement with Palareti's personal views, who explained the difficulty in clinical practice of diagnosing DVT and informing a patient without then giving him appropriate therapy [24].

Finally, a recent study (Cleveland Clinic Experience) including 1100 patients concluded that cancer patients with isolated distal DVT have similar outcomes as their proximal counterparts [25]. This is why we support the necessity of further studies, particularly in high-risk patients with multiple distal DVT.

Limitations

We think that the major limitation of this study is the lack of a control group who did not receive the treatment. However, guidelines for management of distal DVT in our hospital suggest anticoagulant treatment, and no patient is left untreated. In addition, another limitation is the retrospective nature of the study as well as the limited number of patients included.

Conclusion

This retrospective study including a limited number of patients and no control group supports that a 40-day weight-based LMWH treatment after distal DVT seems to be efficient when one single vein is initially affected whereas for multiple vein distal DVT and to avoid potential DVT recurrence, longer than 6 weeks of anticoagulant treatment is required. Our results support safety of the treatment, its potential to prevent DVT extension and the occurrence of PE.

Compliance with ethical standards

Conflict of interest The authors state that they have no conflict of interests.

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