



Venous Thrombosis in Patients Presenting with Cellulitis of the Lower Limbs

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Abstract

Background: Lower limb cellulitis shares many of the features of deep vein thrombosis. Venous Doppler ultrasound examination of the affected leg is frequently performed.

Aim: To estimate the incidence of deep vein thrombosis in intermediate to high risk patients with lower limb cellulitis.

Design: Prospective study of patients admitted for cellulitis.

Methods: We screened 372 patients sequentially admitted for lower limb cellulitis, out of which we enrolled all 68 patients above 18 years old who were hospitalized for 3 or more days and had at least intermediate risk for Deep Vein Thrombosis (DVT) by Wells' criteria. The operator of the Doppler duplex ultrasonography was blinded to patient characteristics, clinical course and Wells' score.

Results: Of the 68 patients, we detected two patients with deep vein thrombosis (2.9%, 95% CI 0-6.8%), significantly lower than the expected 17% based on the Wells' score ($p<0.001$). Three additional patients had Superficial Vein Thrombosis (SVT) (4.4%, 95% CI 0% to 9.2%). The number of patients to be tested in order to diagnose either DVT or SVT is 13 to 16. Four patients with either deep or superficial vein thrombosis required anticoagulation and only immobilization was identified as a significant risk factor (i.e., present in 100% versus 44% of un-treated patients, $p<0.001$).

Conclusion: In patients with cellulitis of the lower limb, the Wells' score overestimates the risk for DVT. Ultrasonography should be limited to patients with high clinical suspicion of DVT and moderate-to-high risk estimation of DVT by Wells' criteria.

Keywords: Cellulitis; Erysipelas; Deep vein thrombosis; Superficial vein thrombosis; Wells' score; Doppler duplex ultrasound

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Introduction

Lower Limb Cellulitis (LLC) is a clinical diagnosis that shares many of the features of Deep Vein Thrombosis (DVT) [1]. Although no significant DVT was found in 245 patients with LLC referred for Doppler duplex ultrasound of the lower limbs, up to 20% of patients presenting to the emergency department with suspected LLC are referred to the vascular laboratory [2,3]. Therefore the need for pursuing the diagnosis of DVT in patients with Lower Limb Cellulitis (LLC) is not well defined.

The Wells' score has been validated to predict the likelihood of DVT in symptomatic patients, but its usefulness in patients with LLC has not been thoroughly studied in patients presenting with overlapping clinical features [4].

The purpose of our study was to determine the incidence of DVT in patients with LLC with an intermediate or high risk for DVT by Wells' score. We also intended to assess the need to test for DVT in the presence of LLC and to identify factors associated with the coexistence of both entities.

Materials and Methods

This observational study was conducted in a 1000 bed, university-affiliated general hospital in Jerusalem, Israel. During a 2.5 year period, all patients diagnosed with Lower Limb Cellulitis (LLC), consecutively admitted to medical departments were screened for inclusion and exclusion criteria.

Table 1: Demographic and clinical characteristics of patients with lower limb cellulitis with and without Deep Venous Thrombosis (DVT).

Demographic and Clinical Characteristics	DVT (N=2)	No DVT (N=66)	Treated (N=4)	Not Treated (N=64)
Age (mean ± SD)	3.5 ± 78.5	14.6 ± 68.4	15.3 ± 77.5	14.6 ± 68.5
Female	50%	48%	75%	45%
Hospital day (mean ± SD)	3.5 ± 8.5	7.5 ± 3.1	3.6 ± 9	3.1 ± 7.45
D-Dimer (ng/mL; mean ± SD)	1166^	1551 ± 2672	2600 ± 2671	2661 ± 1481
Initial WBC (cells/UL; mean)	353 ± 19450	12775 ± 5975	4921 ± 15500	6048 ± 12812
ERS (mm/H; mean ± SD)	69^	79 ± 34	13 ± 88	35 ± 79
Previous DVT/PE	1 (50%)	5 (8%)	1 (25%)	5 (8%)
Active Malignancy	0 (0%)	2 (3%)	0 (0%)	2 (3%)
Immobilization	2 (100%)‡	30 (46%)	4 (100%)‡	28 (44%)
Hypercoagulability	0 (0%)	2 (3%)	0 (0%)	2 (3%)
Chronic leg edema	0 (0%)‡	29 (44%)	2 (50%)	27 (42%)
Fever >37.5	2 (100%)‡	44 (67%)	3 (75%)	43 (67%)
Localized tenderness	1 (50%)	32 (49%)	2 (50%)	31 (48%)
Entire leg swelling	1 (50%)	49 (74%)	3 (75%)	47 (73%)
Calf swelling >3 cm than asymptomatic leg	2 (100%)	61 (92%)	4 (100%)	59 (92%)
Pitting edema	2 (100%)	64 (97%)	4 (100%)	62 (97%)
Superficial collateral veins (non varicose)	0 (0%)‡	12 (18%)	0 (0%)‡	12 (19%)

ESR=erythrocyte sedimentation rate; DVT=deep vein thrombosis; PE=pulmonary embolism. Treated refers to patients who received anticoagulation for DVT or SVT. *P<0.05; **P<0.01; ‡P<0.001; ^data for only one patient.

The diagnosis of LLC was based on at least three of five local signs of inflammation: redness, heat, swelling, pain and limitation of motion.

Inclusion criteria consisted of (1) clinical confirmation of the diagnosis of LLC based on appearance of the affected leg; (2) two out of three of the following; leukocytosis, fever and an elevated erythrocyte sedimentation rate; (3) an expected hospitalization of at least 3 days. Exclusion criteria consisted of age <18 years, a history trauma prior to onset of cellulitis, ulcer cruris or diabetic foot infections, a low probability risk according to Wells' score, or chronic anticoagulation [4].

Complete blood count and erythrocyte sedimentation rate were performed on admission in all patients, and a D-Dimer in 78% of patients. A latex enhanced immunoassay (HS by HemosIL® on ACT TOP®) was used for D-dimer quantification. Venous Doppler Ultrasound examination (US) of the involved leg was performed at least three days after admission or after the onset of initial symptoms. Compression ultrasound, duplex ultrasound and color Doppler imaging of the entire venous tree were performed using an Acuson SEQUOIA 512 with 6L3 linear array transducer (Acuson, Mountain view, CA, USA). Superficial veins were also examined routinely. One of the authors (DS) blinded to patient data interpreted US and diagnosed DVT using previously described criteria [5].

Considering an incidence of DVT above 17%, a sample of 61 patients was required to reach significant results with type I error of 5% [4]. Comparisons of variables between DVT versus no-DVT patients, and treated (with anticoagulation) versus not treated patients were performed. Two sided t-test (after testing for variance comparisons) and Z-test were applied when appropriate. The conduct of this study was approved by the hospital Internal Review Board.

Results

Of the 68 patients enrolled, 51% were female, and the mean age was 69 years. Two patients developed DVT (2.9%, 95% CI [0% to 6.8%]) and three had Superficial Vein Thrombosis (SVT) of

saphenous veins (4.4%, 95% CI [0% to 9.2%]) accounting for five thrombotic events (7.3%, 95% CI [1.1-13%]), of whom four required anticoagulation (5.9%, 95% CI [3% to 11%]). Of the five patients with thrombotic events, two with DVT and one with great saphenous SVT were discharged with anticoagulation therapy. One patient diagnosed with SVT of the lesser saphenous vein with expansion to the popliteal vein was treated with enoxaparin only during his hospitalization. One patient had chronic venous insufficiency and an old femoral vein thrombosis.

A history of immobilization was present in all patients with DVT or those requiring anticoagulation, and present in 44% to 46% of their counterparts ($p<0.001$) (Table 1). Co-morbidities included: Cardiovascular disease (62%), obesity (44%), diabetes mellitus (24%), orthopedic disease (22%), recurrent cellulitis (15%), pulmonary disease (15%), renal failure (12%), and chronic venous insufficiency (2%).

Discussion

This are only several observational studies in the literature that assess the incidence of DVT in patients with LLC, making these results relevant for routine clinical practice [1,6-8]. The incidence of DVT in this study was 3%, lower than the expected 17% prevalence for intermediate risk population according to the Wells' score ($p<0.0001$). This finding is even more significant since 59% of our patients had a high probability Wells' score. This discrepancy could be explained by the overlapping clinical signs of LLC and DVT. Therefore, the clinical criteria used to calculate the Wells' score may not help to discriminate between these two clinical entities. Our results are in accordance with those of a recent review of the literature that included heterogeneous studies that systematically investigated for the presence of DVT in LLC, with an incidence of 0% to 10% (overall rate of 2.72%) [6]. Other prospective studies by Perrot et al., [7] and Bersier and Bounameaux, reported a similar incidence of 2.6% and 1.6% respectively [1].

Two of our patients with SVT received anticoagulation in accordance with standard clinical practice as proposed by Decousus et

al., [7]. Based on the number of patients who required anticoagulation after performing ultrasound, we estimated that the number of tests needed to be performed in order to detect one treatable vein thrombosis would be 17 to 19. This number could be further reduced in the presence of a positive D-Dimer test.

In our study, patients with either DVT or SVT were immobilized for at least three days. Bersier and Bounameaux also found that immobilization was the most significant risk factor for DVT in patients with LLC (57%) [1]. We estimated that if only immobilized patients with LLC would undergo ultrasound, we would need to test 9 patients to detect a single thrombotic event. At first glance, the incidence of DVT in LLC is too low to justify obtaining a duplex ultrasound, since according to our results we would have to test 295 immobilized patients similar to those in our study to prevent one death (considering a 3% probability of fatal venous thromboembolism in patients with DVT) [9]. A recent and similar study found a 1.5% prevalence of DVT in 200 patients presenting with LLC; however, only 31 (15.5%) could be considered to have a high pretest probability for DVT (i.e., high Wells' score and positive D-Dimer test) [8]. Only one of the 31 patients (3.2%) with a high pretest probability was diagnosed with a DVT, an incidence similar to what we observed.

To the best of our knowledge, this is the largest observational study of patients with LLC and intermediate to high pre-test probability for DVT. We are aware that our small sample size precludes an accurate estimate of the real incidence of DVT in these patients. Another limitation of our study was the lack of follow up of the patients after discharge, theoretically resulting in an underestimation of the incidence of DVT in patients with ongoing risk factors. Finally, our results may be generalizable only to patient populations with advanced age and multiple co-morbidities.

Conclusion

We observed that the Wells' score overestimates the risk for DVT in patients presenting with LLC. However, it seems appropriate to perform Doppler duplex examination for venous thrombosis in patients with lower limb cellulitis, intermediate to high Wells' score, and a history of immobilization for at least three days. Further prospective randomized studies are needed to further substantiate these findings.

Summary

- Why is this topic important? Lower limb cellulitis shares many of the features of deep vein thrombosis. Venous Doppler ultrasound examination of the affected leg is frequently performed.
- What does the study attempt to show? To estimate the incidence of deep vein thrombosis in intermediate-to-high risk patients with lower limb cellulitis.

- What are the key findings? We screened 372 patients sequentially admitted to the emergency department for lower limb cellulitis, out of whom 68 patients >18 years old who had at least intermediate risk for Deep Vein Thrombosis (DVT) by Wells' criteria. Of these 68, 2 patients were diagnosed with DVT (2.9%, 95% CI 0% to 6.8%), significantly lower than the expected 17% based on the Wells' score ($p<0.001$). Three additional patients had Superficial Vein Thrombosis (SVT) (4.4%, 95% CI 0% to 9.2%).

- How is patient care impacted? In patients with cellulitis of the lower limb, the Wells' score overestimates the risk for DVT. Ultrasonography should be limited to patients with high clinical suspicion of DVT and moderate-to-high risk estimation of DVT by Wells' criteria.

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