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Factors related to deep vein thrombosis in patients with cellulitis/erysipelas at two high-complexity facilities

A case-control study

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Abstract

Lower extremity venous thromboembolism in the presence of soft tissue infection (cellulitis/erysipelas) is difficult to diagnose using clinical findings alone. This leads to an overuse of Doppler ultrasound, which is unnecessary in many cases. In Colombia, there are no studies to date reporting the simultaneous prevalence of these two conditions.

Objective: to determine which factors are related to deep vein thrombosis in patients with lower extremity cellulitis/erysipelas.

Materials and methods: a case-control study. Patients seen at Hospital Pablo Tobón Uribe and the university hospital between January 2018 and December 2019 who were diagnosed with cellulitis/erysipelas and underwent lower extremity venous Doppler. Demographic, clinical, laboratory and imaging variables were considered.

Results: altogether, 637 patients with a diagnosis of lower extremity cellulitis and erysipelas were found during the study period in both institutions. Of these, 18.5% (118 patients) had a lower extremity Doppler ultrasound ordered to rule out deep vein thrombosis, finding a total of 25 positive studies (21.19%). Out of the total sample, 56 (47.4%) were male, with a mean age of 65 years. Most of the cases (55.08%) had an intermediate risk according to the Wells scale. The most common patient factors related to thrombosis were: immobility 33%, lymphedema 29.66%, and chronic kidney disease 23.73%. Neoplasms were the factor which showed statistical significance for the presence of thrombosis OR 5 (1.64-15.16) (P=0.0056).

Conclusions: cellulitis is not a unique finding to justify carrying out a Doppler test, and the routine use of this imaging technique in the diagnostic approach is not justified if there are no other risk factors for thrombosis. **(Acta Med Colomb 2022; 47. DOI: https://doi.org/10.36104/amc.2022.2109).**

Keywords: *deep vein thrombosis, cellulitis, erysipelas, risk factors*.

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Introduction

Deep vein thrombosis (DVT) of the lower extremities is a highly morbid condition which leads to complications like secondary pulmonary embolism and post-thrombotic syndrome, with the main risk factors described being a hypercoagulable state, family history of thrombosis, vascular wall injury, surgery, immobility, active cancer, age, obesity, hospitalization, and the use of estrogen and progesterone (1, 2). Doppler ultrasound of the lower extremities is the standard diagnostic test as it has good sensitivity and specificity and is noninvasive. However, the current problem is overuse of this tool without an adequate correlation between the clinical findings and DVT risk factors to justify its use (3, 4).

The clinical findings in lower extremity cellulitis/erysipelas and extremity DVTs are similar and, in most cases, unclear. In both situations there is calf pain, edema or sensitivity, erythema and hardening of the skin with occasional changes in coloring, which makes it difficult to distinguish one condition from the other based solely on the physical exam. It is common for many patients admitted with a diagnostic suspicion of cellulitis/erysipelas (CE) to undergo Doppler ultrasound of the lower extremities to assess for the presence of concomitant DVT, a test which is very rarely positive. This suggests that the clinical predictors are not very specific, and this diagnostic tool is overused, with a high percentage of inconclusive results which are not use-

ful and, on the contrary, increase healthcare costs (3). The objective of this paper was to determine which factors related to deep vein thrombosis in patients with lower extremity cellulitis/erysipelas justify performing Doppler imaging. The hypothesis is that a history of conditions related to hypercoagulability and venous stasis are the most significant risk factors for DVT in CE.

Materials and methods

A case-control study was performed including patients over the age of 18 who were seen in the emergency room with a diagnosis of lower extremity CE and underwent Doppler between January 2018 and December 2019. Patients with the complication of necrotizing fasciitis were excluded. Cases were defined as patients diagnosed with lower extremity CE with a documented DVT on Doppler. Controls, in turn, were defined as patients diagnosed with CE who underwent Doppler for suspected DVT, but whose study was negative for thrombosis.

A simple randomized probabilistic sample was calculated, considering the most common antecedent in prior studies: DVT, with a case prevalence of 44%. A 95% confidence interval, 80% power, 0.05 error, 1:4 case-control ratio and odds ratio (OR) of 5 required a total of 95 patients: 19 cases and 76 controls.

A pilot study was conducted initially to document the frequency of Doppler tests in the patients and a complete description of the study variables.

For bias control, a representative sample of the population, with a different severity but during the same period of time, was included, incorporating those admitted to the emergency room and hospital wards. Each investigator reviewed each institution's information and recorded variables.

Analysis plan

Using a Microsoft Excel database, data analysis was performed with the Epi Info 7.2.4 program.

Univariate analysis: a table of frequencies was constructed describing the mean and standard deviation for quantitative variables, and absolute and relative frequencies for qualitative variables.

To compare the groups of patients with and without DVT in the bivariate analysis, Chi square or Fisher's exact test were used for qualitative variables, and the OR was calculated with its respective confidence interval. The level of statistical significance was a P less than 0.05. The only quantitative variable was age, and this was not included in the bivariate analysis. Logistic regression was run to determine the effect of confounding variables and those related to the dependent variable DVT.

Results

A total of 637 patients were found with a diagnosis of lower extremity CE between 2018 and 2019 in both institutions. Of these, 118 patients had a lower extremity Doppler ordered, finding a total of 25 positive cases for DVT (21.19%). The demographic, clinical and laboratory characteristics of both groups are described in Table 1. The most prevalent clinical sign was extremity pain in 95.76% of the patients, followed by extremity asymmetry in 88.14% and unilateral edema in 79.66%. Fever only occurred in 33.05%. The Wells scale was not calculated in 11 cases, with most cases (55.08%) having an intermediate risk.

Patients were divided into those with and those without DVT. A bivariate analysis was then carried out to compare the DVT risk factors in both groups, finding an increased risk not due to chance for a history of cancer, with an OR of 5 (1.64-15.16) (P= 0.0056). None of the other clinical or laboratory variables showed a statistically significant difference, although it is worth noting that a history of peripheral neuropathy had an OR of 6.2 with a lower limit of the confidence interval very close to the unit, but not statistically significant (0.97-39.41) (P= 0.063). Likewise, limb erythema had an OR of 0.16 (0.02-1.02) (P=0.063) with the upper limit of the interval close to 1 (Table 2).

For the logistic regression analysis, the effect of variables related to a known history of conditions that increase the probability of venous thromboembolic disease such as: a history of immobility, cancer, use of hormone therapy, personal history of DVT, and peripheral neuropathy was established with a 95% confidence level; as was the effect of potentially confounding variables related to physical exam findings: extremity erythema, not including those with probable collinearity such as asymmetrical edema and extremity pain. The DVT-related factors which showed a statistically significant difference were hormone therapy, with an OR of 18.08 (1.43-228.11), a history of cancer with an adjusted OR of 5.67 (1.68-19.09), and peripheral neuropathy with an adjusted OR of 9.36 (1.36-64.47). No relationship was found with limb erythema, with an OR of 0.10 (0.01-0.88) (Table 3).

Discussion

The prevalence of DVT in concomitant cellulitis or erysipelas ranges from 0-15% (5, 6). We found a percentage slightly greater than 21%. Maze et al. reported 15% of patients with cellulitis who underwent Doppler, of whom only 0.5% were positive for DVT (7), and a systematic review and a meta-analysis published in 2013 included 1,054 patients with cellulitis/erysipelas, of whom 18 had DVT, with a general incidence rate of 2.1%, but all showed a low concurrence of both conditions (8). In addition, we found that Doppler ultrasound was performed in 18.5%, similar to and even lower than what was reported in other articles. Afzal et al. published a retrospective study in patients with extremity cellulitis in whom the percentage of Doppler tests performed was close to 70%, with only 6% of these positive for DVT (4). This shows that this diagnostic tool is also overused in our setting, increasing unjustified costs for the healthcare system.

Table 1. *Patients' demographic and clinical characteristics (n= 118).*

Variable	N/ Frequency % / Mean (SD)
Sex, Male (%)	56 (47.46)
Age in years	65 (45-85)
Positive D-dimer	14 (11.86)
Elevated CRP	63 (53.38)
Leukocytosis	29 (24.58)
Neutrophilia	31 (26.2)
Skin lesions	30 (25.42)
Fever	39 (33.05)
Edema below the knee	80 (67.80)
Edema above the knee	16 (13.56)
Edema above and below the knee	8 (6.78)
Erythema of the extremities	113 (95.76)
Unilateral extremity edema	94 (79.66)
Asymmetrical extremities	104 (88.14)
Pain in the extremities	113 (95.76)
Joint pain	19 (16.10)
Venous cord pain	15 (12.71)
Collateral circulation	16 (13.56)
High Wells risk score (3 or more points)	35 (29.66)
Moderate Wells risk score (1-2 points)	65 (55.08)
Low Wells risk score (0 points)	7 (5.93)
Use of hormone therapy	3 (2.54)
Obesity	17 (14.41)
PH PTE	2 (1.69)
PH CHF	21 (17.80)
PH COPD	14 (11.86)
PH CVA	10 (8.47)
PH DM	23 (19.49)
AP HIV	1 (0.85)
PH DVT	17 (14.41)
PH extremity trauma	23 (19.49)
PH procedure	23 (19.49)
PH peripheral neuropathy	5 (4.24)
PH lymphedema	35 (29.66)
PH skin lesion	16 (13.56)
PH immobility	39 (33.05)
PH CKD	28 (23.73)
PH cancer	16 (13.56)
PH cellulitis/erysipelas	27 (22.88)
PH cirrhosis	8 (6.78)
PH anticoagulation	12 (10.17)
FH VTE	3 (2.54)

PH: personal history, FH: family history, DVT: deep vein thrombosis, CKD: chronic kidney disease, HIV: human immunodeficiency virus, DM: diabetes mellitus, CVA: cerebrovascular accident, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, PTE: pulmonary thromboembolism, VTE: venous thromboembolism, CRP: C-reactive protein.

Table 3. *Multivariate logistic regression analysis Análisis por regresión logística multivariable.*

Variable	Odds ratio (95% CI)	p
PH DVT	2.29 (0.56-9.29)	0.246
PH cancer	5.67 (1.68-19.09)	0.005
PH immobility	2.04 (0.65-6.33)	0.216
PH neuropathy	9.36 (1.36-64.47)	0.023
PH hormone therapy	18.08 (1.43-228.11)	0.025
Extremity erythema	0.10 (0.01 – 0.88)	0.038

Specifically for lower extremity cellulitis/erysipelas, the risk factors for concomitant thrombosis are not clearly defined, as some have not been shown to be related in the studies, which explains the limited usefulness of the usual clinical prediction models for DVT (4-8). Afzal et al. found that a history of thrombosis, prior cerebrovascular accident, calf edema and hypertension were statistically significant for concurrence of both conditions (4). In our study, we found that a history of cancer was a significant and precise variable for DVT in a cellulitis context. Although it is a known risk factor for thrombosis, its association with concurrent infection had not been shown in other reports (4-8). Likewise, a history of peripheral neuropathy and hormone therapy showed an association on multivariate analysis after adjusting for variables related to DVT. Regarding clinical signs, we did not find that acute phase reactants or inflammatory or measurement changes in the limb were indicative of DVT. This finding was similar to what was reported in other cohorts (8), but it is interesting that, in our study, limb erythema behaved as a factor against a DVT diagnosis, showing statistical significance after adjusting for possible confounding variables, which generates a hypothesis which will need to be confirmed in subsequent studies. While infection may be a risk factor for thrombosis, we found, as did previous articles, that it should not be the only finding to justify performing a Doppler test. Given that the occurrence of both diagnoses together is rare, most authors suggest that, in the absence of known DVT risk factors, routine use of this imaging is unnecessary within the initial diagnostic approach (5-7). As a case-control study, this paper has limitations, as it is subject to selection and information biases, and we cannot determine the percentage of patients with cellulitis who did not undergo Doppler and did have a DVT, which underestimates the incidence of this diagnosis. Also, the study only included two years of follow up at two institutions in the city, with a small sample size, which could explain the lack of association of some of the variables. However, our results are important since they propose an initial idea of the coexistence of these two conditions and potentially

Table 2. *Bivariate analysis*.

Variable	Without DVT (%): total 93	With DVT (%): total 25	Odds ratio (95% CI)	p
FH DVT	2 (2.1)	1 (4)	1.89(0.16 – 21.80)	0.5138
PH DVT	12(12.9)	5 (20)	1.68(0.53-5.34)	0.3531
PH anticoagulation	10(10.7)	2 (8)	0.72 (0.14-3.52)	1.0
PH cirrhosis	6(6.4)	2 (8)	1.26 (0.23-6.66)	0.6762
PH skin infection	24 (25.8)	3 (12)	0.39 (0.20- 1.42)	0.1852
PH cancer	8 (8.6)	8(32)	5 (1.64-15.16)	0.0056*
PH CKD	22 (23.6)	6(24)	1.01(0.36-2.86)	1
PH immobility	29 (31)	10(40)	1.47 (0.59 – 3.66)	0.4744
PH skin lesion	13(13.98)	3(12)	0.83 (0.21-3.20)	1
PH lymphedema	27 (29.03)	8(32)	1.15 (0.44 – 2.98)	0.8075
PH neuropathy	2(2.1)	3(12)	6.20(0.97 – 39.41)	0.0632
PH procedure	18(19.3)	5(20)	1.04(0.34-3.15)	1
PH trauma	20(21)	3(12)	0.49 (0.13-1.83)	0.3979
PH HIV	1(1.08)	0	0	1
PH DM	17(18.2)	6(24)	1.41 (0.49- 4.06)	0.5721
PH CVA	9(9.6)	1(4)	0.38(0.046-3.22)	0.6864
PH COPD	9(9.6)	1(4)	0.38 (0.04- 3.22)	0.6864
PH CHF	17(18.2)	4(16)	0.85(0.25- 2.80)	1
PH PTE	2(2.15)	0	0	1
PH hormone therapy	1(1.08)	2(8)	8 (0.69-92.11)	0.1131
PH obesity	14(15)	3(12)	0.77 (0.20-2.91)	1
Extremity asymmetry	81(87)	23(91)	1.70 (0.35-8.16)	0.7312
Collateral circulation	12(12.9)	4(16)	1.28 (0.37- 4.39)	0.7436
Venous tract pain	11(11.8)	4(16)	1.41 (0.41-4.91)	0.5198
Extremity pain	89(95)	24(96)	1.07 (0.11- 10.10)	1
Skin lesions	26(27.9)	4(16)	0.49 (0.15-1.56)	0.3035
Bilateral edema	18(78.8)	6(24)	1.31 (0.45- 3.76)	0.5862
Unilateral edema	75(80.6)	19(76)	0.76 (0.26-2.17)	0.5862
Edema extension	NA	NA	NA	0.1422
Extremity erythema	91(97.8)	22(88)	0.16 (0.02-1.02)	0.06326
Fever	32(34.4)	7(28)	0.74 (0.28-1.95)	0.6366
Tachycardia**	4(4.3)	2(8)	NA	0.1122
Leukocytosis**	23(24.7)	6(24)	NA	0.9451
Neutrophilia**	24(25.8)	7(28)	NA	0.9451
CRP**	15(16)	3(12)	NA	0.2265
D-dimer **	NA	NA	NA	08687

**p<0.05 significant at two tails using Fisher's exact test*
***Qualitative polytomous variables calculated through Chi²*
NA: Not applicable
PH: personal history, FH: family history, DVT: deep vein thrombosis, CKD: chronic kidney disease, HIV: human immunodeficiency virus, DM: diabetes mellitus, CVA: cerebrovascular accident, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, PTE: pulmonary thromboembolism, CRP: C-reactive protein.

related factors, and provide guidelines to improve clinical practice with an appropriate use of this resource.

Conclusions

- The finding of cellulitis alone does not justify performing a Doppler, and the routine use of this imaging within the diagnostic approach is not justified if there are no other risk factors for thrombosis.
- This paper suggests that a history of cancer, peripheral neuropathy and hormone therapy are clinical predictors of associated DVT in the context of soft tissue infection, which can be taken into account in daily practice.
- We hypothesize possible variables related to the concomitant presence of DVT in cellulitis, but additional prospective studies are needed to validate these findings.

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References

1. **Kahn S, Lim W, Dunn A, Cushman M, Dentali F, Akl E Et al.** Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;**141(2 Suppl):** e195S-e226S
2. **Di Nisio M, van Es N, Büller H.** Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;**388(10063):**3060-3073
3. **Heit J, Spencer F, White R.** The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016;**41(1):**3-14.
4. **Afzal M, Saleh M, Razvi S, Hashmi H, Lampen R.** Utility of Lower Extremity Doppler in Patients with Lower Extremity Cellulitis: A Need to Change the Practice? *South Med J* 2015 Jul;**108(7):**439-44
5. **Bersier D, Bounameaux H.** Cellulitis and deep vein thrombosis: a controversial association. *J Thromb Haemost* 2003;**1:**867Y868
6. **Bendick P.** Cellulitis and the prevalence of deep vein thrombosis. *J Diagn Med Sonog* 1996; **12:**170-74
7. **Maze M, Skea S, Pithie A, et al.** Prevalence of concurrent deep vein thrombosis in patients with lower limb cellulitis: a prospective cohort study. *BMC Infect Dis* 2013; **13:**141.
8. **Gunderson C, Chang J.** Risk of deep vein thrombosis in patients with cellulitis and erysipelas: a systematic review and meta-analysis. *Thromb Res*. 2013;**132(3):**336-40.