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REVIEW ARTICLE

Calf Deep Venous Thrombosis : A Review of the Literature

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Introduction

Calf deep vein thrombosis (DVT) still remains a debatable entity in terms of its clinical importance and its management. Minimal, non-obstructive calf vein thrombi that are asymptomatic, are encountered up to 30% in hospitalised or postoperative patients after surveillance investigation by radioactive fibrinogen leg scanning or venography.[1,2] It has been stated that calf deep vein thrombi become clinically important only when they extend into the proximal veins.[3] However, untreated asymptomatic calf DVT might carry a 2% incidence of fatal pulmonary embolism (PE) in bedridden immobile patients, based on a 20% rate of propagation of calf thrombi.[4] Similarly, it is debated whether untreated isolated calf thrombosis causes post-thrombotic syndrome unless proximal extension occurs.[5] Nevertheless, abnormal venous function has been reported after asymptomatic[6,7] and symptomatic[8,9] calf DVT. It has been estimated that the risk of the post-thrombotic syndrome resulting from untreated asymptomatic calf DVT would be approximately 4%, based on a 20% rate of extension of calf thrombi.[4]

Symptomatic calf DVTs are usually found in association with thrombosis in the more proximal veins. The incidence of isolated symptomatic calf DVT is unclear, with reports suggesting rates varying from 9 to 46%.[10–13] However, the isolated symptomatic calf thrombi are probably larger than the asymptomatic[13–15] and so are more likely to cause complications.

The management of calf DVT is based on comparing its risk of early complications with the risk of anticoagulation. Bleeding complications, particularly in elderly and postoperative patients can be a source of significant morbidity and many would argue that such treatment is not justified when the risk of pulmonary embolism is low. The advent of sophisticated non-invasive techniques for diagnosing DVT, may now make it possible to be more selective in identifying those patients with calf DVT who should be treated.

In this review, we wish to set out logical guidelines for the management of calf DVT, using non invasive imaging techniques, based on what is known about its natural history, complications, and treatment.

Origin of Deep Venous Thrombosis

The origin of DVT in the lower limb has been a subject of considerable controversy. It is now known that the vast majority of the thrombi commence in the deep calf veins,[16–19] but it is apparent that acute DVT can start anywhere in the venous system, including the proximal veins of the leg and pelvis.[18–21] However, it has been shown, with few exceptions, that whenever there are thrombi in the proximal veins, there are always thrombi present in the calf veins.[10,18,22–24]

The incidence of isolated symptomatic calf DVT is unclear. Philbrick and Becker,[26] in a review of 20 studies including 2140 patients (medical and surgical)

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where DVT was documented by venography, reported a 48.8% incidence of calf DVT. In two other studies[10,11] including 327 limbs with DVT detected by venography the incidence was 46%, and in another one[27] including 24 patients with DVT detected by Duplex ultrasonography was 37.5%. Markel *et al.*[12] reported that isolated calf DVT was 9% in their series.

The distribution of DVT it is said to be more or less similar in both the surgical and medical patients.[3,10,23,24,28,29] Also, in another study the origin and the distribution of DVT in symptomatic ambulatory patients was equivalent to that in inpatient population.[16] However, the majority of these studies included a mixed population (medical and surgical) and it is not completely clear whether the studied individuals were ambulant or immobile, inpatients or outpatients, and the kind of the operation or illness they experienced since there is no adequate description on the patient demographic data. Therefore, it is apparent that, the true incidence of calf DVT in different groups and subgroups of patients is very difficult to be evaluated precisely.

Natural History

Thrombi in the calf veins either may lyse spontaneously, or recanalise over several weeks or months. Alternatively, they may stay localised to the calf or extend up to the proximal veins of the leg. Recurrence is also commonly seen.

(A) Lysis and recanalisation of deep venous thrombi

It is known that immediately after the occurrence of DVT collateral circulation develops to bypass the obstruction and to provide a fair venous outflow.[31] Lysis of the thrombi can occur at any time, from some hours to months after the occurrence of the thrombosis.[3,32] Kakkar *et al.*[3] reported that in their series including postoperative patients one third of the acute thrombi lysed within 72 h and these thrombi obviously would never be picked up by clinical assessment. Spontaneous lysis of the thrombi might be a result of the local fibrinolytic activity (plasminogen activator release).[25]

(B) Proximal extension of calf thrombi

Proximal propagation of the thrombi can occur, and sometimes this may happen in a late period after the initial diagnosis of DVT.[33] Browse and Thomas[28] have estimated in their series that two-thirds of the thigh and one-half of the pelvic thromboses were due to propagation of the calf DVT. The incidence of proximal extension of the calf thrombi in postoperative patients varies from 5.6% to 30%[3,26,30,34,35] with a 10% propagation rate in symptomatic patients.[9] Asymptomatic calf vein thrombi, detected by radioactive fibrinogen leg scanning, extended into the proximal veins in 20% of cases.[3] In another study,[36] 75 medical and surgical patients, with isolated calf vein thrombi were prospectively monitored with sequential Duplex scans at 3- to 4-day intevals, 24 of the patients (34%) had a thrombus propagation into the proximal veins. In this study, sex, age, obesity, trauma, estrogen use, malignancy, varicose veins, smoking, surgery, and activity level were not predictive of propagation. However, it is still not known whether factors such as blood transfusion, the type and duration of surgery or anesthesia may interfere to calf vein thrombi propagation.

The pattern of thrombus propagation still remains unresolved. From necropsy studies[20,21,33] we know that thrombosis may be present at different sites in the venous tree of the lower limb with evidence that propagation can occur in either a proximal or distal direction. Other clinical studies have shown that the vast majority of thrombi commence in the calf veins and extend proximally by forming a continuous column of thrombus.[1,28,37–41] Today, the pattern of antegrade proximal extension of the calf thrombi is well established and widely accepted.

Prophylaxis with low doses of heparin significantly reduces both the incidence and the proximal extension of the DVT. In a review of four large studies[35,42–44] including 3116 patients undergoing elective abdominal operations, 95 (6.4%) out of 1485 patients in heparin group had thrombosis, and proximal extension occurred only in nine (0.6%) patients. On the other hand, in the control group 380 of 1631 (23.3%) patients had calf DVT and proximal extension occurred in 99 (6%) patients. This finding is supported in a study of 78 patients undergoing total hip or knee arthroplasty, where Barnes *et al.*[45] reported proximal extension of isolated calf DVT in 18% of patients who did not receive anticoagulation. In another study[27] evaluating 24 patients with acute DVT using Duplex ultrasonography, nine patients (37.5%) had thrombosis confined to the calf veins and four had progression of thrombosis at the proximal veins despite being on anticoagulant treatment. There was no difference in the anticoagulation level between propagators and non-propagators and of the demographic and clinical

variables examined, only smoking correlated with progression of thrombus. These results raise quite interesting questions.[46] Will some patients with DVT have proximal extension of the thrombi regardless of their adequate anticoagulation level with heparin as other studies have shown on venography that up to 20% of patients with DVT will experience deterioration receiving heparin.[47] The ideal amount of heparin given to patients with DVT should be the lowest dose that prevents the proximal extension of thrombosis.[48] However, this dose has not yet been established. Also, there is no information in the existing literature regarding the factors that could identify the high risk patient in whom extension of thrombosis in to proximal veins from the calf could be anticipated.

(C) Recurrence of deep venous thrombosis

A previous history of thrombosis is one of the major predisposing factors for recurrent DVT in both ambulant and bedridden patients,[17,49,50] and the calf veins are the most frequently affected. Rollins *et al.*[51] reported that all limbs with recurrent acute DVT had evidence of previous calf thrombi, and only 13% had previous proximal disease. In another study,[18] 54 of the 80 limbs (67.5%) with DVT had evidence of a recurrence involving the calf veins and/or the proximal veins. In patients with symptomatic calf DVT, a 29% rate of recurrence has been reported without adequate anticoagulant treatment.[52] This recurrence was prevented in 96% with orally given anticoagulant treatment for 3 months.[53]

(D) Pulmonary embolism from calf thrombi

The concept that calf vein thrombi are asymptomatic and clinically unimportant and that only when they extend to the proximal veins can lead to PE, has been a general impression held by many clinicians. Kakkar *et al.*[3] reported 10% incidence of PE in postoperative patients with asymptomatic calf DVT detected by radioactive fibrinogen leg scanning but in these cases the calf vein thrombi had extended into the proximal veins before the PE become obvious. However, in a comprehensive review of the literature, it was pointed out that DVT confined to the calf alone is not always a benign condition, and incidence of PE as high as 29% have been related including two fatal events.[26] Moreno-Cabral *et al.*[41] examined 54 patients with positive venograms showing DVT either in the calf and/or popliteal veins. In these series, popliteal and calf thrombi had a 66% and 33% incidence of PE respectively, identified by changing V-Q imbalance on serial scans, or positive pulmonary angiogram. These findings support the impression that thrombi become more dangerous when they extend into the popliteal vein. Nevertheless, the incidence of PE associated with calf DVT was relatively high and not be ignored, although most of the emboli arising from the calf veins in these series were silent. Browse and Lea-Thomas[28] have reported that in a series of 201 patients with PE in 53 (26%) the source of the emboli were the calf veins. Barnes *et al.*[45] reported that, isolated calf thrombi accounted for the only two cases of PE in their series of 78 patients with perioperative asymptomatic DVT. In two other studies,[36,52] the rate of fatal PE arising from the deep calf veins was 15% and 13% respectively. Indeed, Dorfman *et al.*[54] performed ventilation-perfusion scans in 58 patients with venographically proven DVT in a prospective study to determine the prevalence of occult PE. They found that all nine patients with below-knee DVT alone had low-probability abnormal scans, while of the other 49 with above-knee DVT, 12 had normal scans, 17 had low-probability scans, three had moderate or undetermined scans, and 17 had high-probability scans.

Therefore, it is apparent that calf deep vein thrombi do cause PE. However, in the majority of the reported cases, the PE was not associated with any clinical signs, and was only detected by lung scans.

It is very important to take into account that many of the reported cases with calf deep vein thrombi are asymptomatic and detected by radioactive fibrinogen leg scannings performed as surveillance for research purposes and otherwise these could have been missed. Also, it is fairly logical to say that many of the reported PEs due to calf DVT could not have been picked up without a lung scan and obviously their clinical significance is unknown. An additional point should be made in regard to the method that was being used in the majority of studies in the diagnosis of PE. It is known that accurate diagnosis can be made only by pulmonary angiography. Lung scan can overdiagnose PEs and this might account for a falsely increased incidence of PE in many studies. Therefore, it is very difficult to estimate precisely the prevalence of PE from thrombi confined to the calf deep veins alone. Furthermore, in many studies it is not known whether proximal propagation of the calf thrombi had occurred before the onset of the PE in patients with previously venographically diagnosed calf DVT. The impression that the majority of thrombi confined to deep veins in the calf are clinically unimportant even

if they cause asymptomatic PE, still remains. Symptomatic calf thrombi, that are larger and tend to extend into the proximal veins, are more likely to be the hazardous ones causing clinically important pulmonary embolism.[4] Thus, it would appear that if we can identify early those by symptomatic thrombi with high probability to propagate proximally early anticoagulant treatment should be instituted.

(E) Post-thrombotic sequela of calf deep vein thrombosis

Once again, there is a common belief that small calf deep vein thrombi do not precipitate post-thrombotic syndrome unless they extend into the proximal veins. It is anticipated that the risk of the post-thrombotic syndrome resulting from untreated asymptomatic calf DVT would be approximately 4%, if one allows for a 20% rate of extension of calf thrombi.[4] However, Lindhagen *et al.*[55] reported that long-term post-thrombotic syndrome after calf DVT occurs as often as it occurs after more proximal DVT. Browse and Clemenson[7] reported that of 61 patients who had calf deep vein thrombi detected by leg scanning associated with mild calf symptoms, 21% had persistent pain and 23% persistent swelling 3–4 years later, but leg symptoms were also similar in patients with negative leg scans. Browse *et al.*[8] suggested a 20% incidence of moderate to serious post-thrombotic syndrome 5–10 years after symptomatic calf DVT. However, this evaluation was made only on the basis of clinical assessment alone and did not include any haemodynamic measurements. Five years later, Kakkar and Lawrence[9] reported 38% mild to moderate and 15% severe haemodynamic changes 6 months after calf DVT using foot volumetry. These abnormalities remained almost unchanged at 2 years. Since then many other authors have also confirmed that long term symptoms and haemodynamic changes are significant complications after calf DVT.[5,6,56]

Diagnosis of Calf Deep Vein Thrombosis

The clinical diagnosis of DVT in symptomatic patients has been shown to be inaccurate in approximately 50% of cases[15,57–59] but the diagnosis of DVT is of paramount importance before treating the patients. Ascending venography is still considered the "gold standard" investigation in the diagnosis of DVT.[60–63] However, this is an invasive technique, exposes the patient to radiation and allergic reactions, causes discomfort, cannot be frequently repeated, and cannot be performed in pregnant women and where there is difficulty in gaining venous access in the foot.

Non-invasive diagnostic modalities that cause less inconvenience to the patients, have been used in the last decade. Gray-scale Duplex imaging and ascending venography were evaluated in a review of 25 studies,[62] including 2781 symptomatic patients. The sensitivity of the Duplex for proximal DVT was 96% while for calf DVT was 80%. Lensing *et al.*[65] showed that the sensitivity of real-time B-mode duplex imaging for isolated calf vein thrombosis was only 36%. This has been confirmed in another two studies[66,67] comparing Duplex and venography in 47 and 68 limbs with suspected DVT respectively. Thus it would appear that Duplex imaging might challenge the ascending venography in the diagnosis of proximal DVT. However, it may miss more than 20% of isolated calf thrombi.[64]

Colour flow Duplex imaging (CFDI) has now emerged as a new more accurate modality in the diagnosis of calf DVT.[68,69] This technique has improved the diagnostic accuracy of isolated calf DVT in symptomatic patients to a 86% sensitivity and 91% specificity.[70] Recently, Bradley *et al.*[71] reported 100% sensitivity and specificity for isolated calf DVT in their series in symptomatic patients. CFDI is now challenging venography as the "gold-standard" investigation for the diagnosis of DVT even in the calf veins.[69] However, the CFDI is not an accurate examination for detection of acute calf DVT in asymptomatic postoperative patients. Rose *et al.*[72] reported 42% sensitivity of CFDI for acute asymptomatic calf thrombi in postoperative patients.

Postoperative asymptomatic calf DVT can be detected by ^{125}I-labelled fibrinogen uptake test (FUT)[1,3] and impedance plethysmography (IPG).[73,74] In 1970's these techniques were accepted enthusiastically as an accurate screening test. Although these methods are considered to be objective their interpretation is in part subjective and as much has serious limitations.[75] Therefore, at present venography still remains the only proven accurate method for the detection of asymptomatic DVT in high risk patients.[75]

Magnetic resonance imaging (MRI) also has been used in the diagnosis of calf DVT in suspected patients with comparable results with ascending venography[76] emerging as another investigation that possibly could replace venography for diagnosis of calf DVT.

Does Calf Deep Vein Thrombosis Require Treatment?

The use of CFDI that can challenge venography in diagnosis and follow-up of calf vein thrombi can offer alternative therapeutic approaches in the management of this problematic area.

There is no agreement on the need to treat calf DVT, especially in asymptomatic cases detected by labeled fibrinogen scanning since these thrombi are considered to be small in size and associated with lower incidence of pulmonary embolism.[77] However, untreated small calf deep vein thrombi that are detected by labeled fibrinogen scanning might cause fatal pulmonary embolism in 2% of bedridden patients and post-thrombotic syndrome in 4%.[4] It has been recommended that only patients with a labeled fibrinogen scanning in the calf persistently positive for more than 48 h receive anticoagulant treatment.[78] Hirsh and Gallus (personal communication) suggested anticoagulant treatment only in the cases that repeated fibrinogen scan indicates proximal extension of the calf deep vein thrombi.[77] So far there is no available data showing the superiority of this approach on treating all patients with calf DVT with anticoagulant treatment.

Moreno-Cabral *et al.*[41] recommended another approach in the management of calf DVT. They advocated treatment with heparin only when the calf thrombi are symptomatic in the legs or when they cause PE, silent of symptomatic. Also, in another study[52] the validity of the anticoagulant treatment (initial course of heparin, warfarin, and compression stockings) in calf DVT *vs.* no anticoagulant treatment (initial course of heparin, and compression stockings) was studied. They found statistical significant recurrence rate of thrombosis with proximal extension in the non-treatment group of patients suggesting that oral anticoagulants should be given for 3 months to all patients with symptomatic calf deep vein thrombi. Lohr *et al.*[36] reported that calf vein thrombi are associated with a 32% incidence of propagation into the proximal veins and a 5% incidence of high probability ventilation perfusion scans. Therefore, they suggested that all calf vein thrombi should be treated with anticoagulation since the risk of bleeding is only 4–10%. Also, they suggested no treatment combined with surveillance by repeat Duplex scanning only in those patients at high risk for anticoagulation. In a review of the literature,[26] the follow-up of the patients with calf DVT by serial IPG and delaying therapy with anticoagulants until propagation has been shown to have occurred, has been supported as it was not clear that calf thrombi had leaded to complications unless they had extended to the proximal veins. Solis *et al.*[79] recently reported that in patients who underwent total joint arthroplasties of the lower extremities, propagation of asymptomatic calf DVT was not influenced by anticoagulation, suggesting that these thrombi should not be routinely treated. Also, they advocated that surveillance by serial Duplex scanning is a useful tactic and anticoagulation should be given only in case of thrombus propagation. The same management of calf DVT is advocated also by Barnes,[80] reserving the anticoagulant treatment only for symptomatic patients, for those with evidence of extension of calf thrombi into the proximal veins, and when clinical PE develops during follow-up. In Table 1 the outcome of calf deep vein thrombosis with or without treatment is displayed. As it is seen in this table, there is no significant difference in the incidence of proximal propagation of the calf thrombi and PE between treated and untreated patients. However, no conclusion can be emerged because these studies were not randomised and prospective and included different patients and treatment protocols each other. Indeed, so far there are not well controlled randomised prospective trials using screening tests or CFDI in patients with thrombi confined to calf veins in order to evaluate the incidence of complications (e.g. PE) and the long term outcome (e.g. post-thrombotic sequela) with different therapeutical approaches.

Nowadays, two approaches seem to be accepted giving a reasonable management in the patients with calf DVT. Heparin and warfarin started at the same time, with heparin discontinued after 4 days and less-

Table 1. Outcome of calf deep vein thrombosis with or without treatment

Author	Year	No patients/ limbs*	Proximal propagation	PE
No anticoagulation				
Kakkar *et al.*[3]	1969	39	9 (23%)	4 (10%)
Doouss *et al.*[30]	1976	124	7 (5.6%)	2 (1.6)
Hull *et al.*[83]	1981	11	0	0
Moser, LeMoine[84]	1981	21	0	0
Lohr *et al.*[36]	1991	75	11 (15%)	4 (5%)
Solis *et al.*[79]	1992	21	2 (9.5%)	0
Barnes[80]	1993	25*	2 (8%)	0
Anticoagulation				
Hull *et al.*[85]	1979	32	0	0
Bentley *et al.*[86]	1980	100	1 (1%)	2 (2%)
Menzoian *et al.*[11]	1983	107	Not studied	4 (3.7%)
Lagerstedt *et al.*[53]	1985	51	Not studied	1 (2%)
Kakkar, Lawrence[9]	1985	98	10 (10%)	Not studied
Schulman *et al.*[87]	1986	36	0	Not studied
Krupski *et al.*[27]	1990	9	4 (44.4%)	0
Solis *et al.*[79]	1992	11	3 (27.3%)	0
Barnes[80]	1993	13*	3 (23%)	0

intense warfarin (international normalised ratio INR = 2.0–3.0) continued for 6 weeks.[21,82] As a reasonable alternative to anticoagulant treatment is considered the surveillance with IPG[4,73,74] or CFDI[4,79,80] for 7–10 days (or longer if the patients remains immobile) and treatment only when there is evidence of thrombus propagation. The latter tactic seems much more reasonable in asymptomatic patients, when the calf thrombus is single and small.

Nevertheless, the management of isolated calf DVT still remains controversial. The efficacy of the proposed tactics for treatment of calf DVT in terms of decrease of the incidence of PE, the recurrence rate, and the long-term post-thrombotic sequela should be evaluated by well randomised prospective trials.

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