Should symptomatic, isolated distal deep vein thrombosis be treated with anticoagulation?

Ashish Anil Sule MD MRCP FICA FAMS¹, Tay Jam Chin FRCP FAMS¹, Pankaj Handa MRCP FAMS¹, Arul Earnest MSc²

AA Sule, TJ Chin, P Handa, A Earnest. Should symptomatic, isolated distal deep vein thrombosis be treated with anticoagulation? *Int J Angiol* 2009;18(2):83-87.

BACKGROUND: During the past two decades, the diagnosis of deep venous thrombosis (DVT) has made considerable progress. The term distal or calf vein thrombosis includes thrombosis in infrapopliteal veins, including the posterior tibial, peroneal, anterior tibial and muscular calf veins. The necessity of treating of distal DVT is debatable.

OBJECTIVE: To determine whether treatment of isolated, distal DVT with anticoagulation versus no treatment affects patient outcome.

METHODS: All patients discharged with a diagnosis of distal DVT from Tan Tock Seng Hospital, Singapore, between January 1, 2006, and December 31, 2007, were identified by the medical records office of the hospital. Compression of the intraluminal thrombus by duplex scan was used to diagnose distal DVT. Excluded were patients who either had both distal and proximal DVT, or had distal DVT along with pulmonary embolism (PE) at presentation.

Complete resolution of distal DVT on repeat duplex scan was used to measure the primary outcome. Repeat follow-up scans were performed at two weeks, one month, three months and six months, or on subsequent follow-up until the distal DVT had resolved completely.

Secondary outcome measures were complete improvement of symptoms, progression of thrombosis, or PE or death during the follow-up period.

The study included 68 patients with distal DVT; however, 17 patients with PE, two of whom had proximal DVT (in the iliac and common femoral veins) at the first presentation along with distal DVT, were

excluded from the study. In total, 51 patients were included for analysis. The follow-up scan was available in 35 patients; therefore, the primary analysis was performed in 35 patients (47 incidences of distal DVT). However, the secondary analysis was available in all 51 patients.

Of the 35 patients available for follow-up scans, 17 patients (25 incidences of distal DVT) received anticoagulation and 18 patients (22 incidences of distal DVT) received no anticoagulation.

Of the 17 patients who were treated with anticoagulation, nine patients (13 incidences of distal DVT) received enoxaparin at a dose of 1 mg/kg twice a day for two weeks and eight patients (12 incidences of distal DVT) received warfarin for a period of three months with initial overlap of enoxaparin 1 mg/kg twice a day for three to five days. Once the prothrombin time international normalized ratio of a patient on warfarin was between 2 and 3, enoxaparin was discontinued. The 18 patients who did not receive anticoagulation received follow-up with regular duplex scan.

RESULTS: There were no statistically significant differences among the groups in the resolution of distal DVT or symptom improvement with or without treatment. In the group that received no treatment, one death occurred. Proximal extension and PE were not recorded in any of the patients.

CONCLUSION: Distal DVT may not require treatment with anticoagulation. If leg symptoms worsen, or if there is an extension of distal DVT on the follow-up scan, treatment with anticoagulation is recommended.

Key Words: Anticoagulation; Distal; DVT; Symptomatic; Ultrasound

During the past two decades, diagnosis of deep venous thrombosis (DVT) or calf vein thrombosis has made considerable progress. Distal DVT is located along the lower leg and includes the infrapopliteal veins, such as the posterior tibial, peroneal, anterior tibial and muscular calf veins (soleal or gemellar). The popliteal vein is not considered distal. Distal DVT is not as common as proximal DVT. In studies including inpatients (1-3), 80% of DVTs were proximal; distal DVTs accounted for only 20%. The natural history of distal DVT, in particular the rate of extension to proximal veins and the embolic potential, is considered nominal compared with proximal DVT. Treatment of distal DVT is debatable when compared with the bleeding risk secondary to anticoagulation (1-3). The purpose of the present study was to determine whether treatment of isolated, distal DVT with anticoagulation versus no treatment affects patient outcome.

METHODS

Medical records from Tan Tock Seng Hospital, Singapore, from January 1, 2006, to December 31, 2007, identified all patients

discharged with a diagnosis of distal DVT. A retrospective analysis of the data for demographic features, management and outcome was performed.

The diagnosis of calf DVT was based on findings of compression of the intraluminal thrombus by duplex scan performed at the vascular diagnostic laboratory of Tan Tock Seng Hospital.

The thrombus was defined as completely resolved when the follow-up scan was normal and partially resolved if the thrombus was smaller but still present; no resolution was defined as persistence of the thrombus, and progression occurred if the thrombus showed extension.

Only patients with a diagnosis of symptomatic, distal DVT were included in the present study. Those who had symptomatic, distal DVT with proximal extension or pulmonary embolism (PE) on presentation, a history of DVT, or those on anticoagulation for any other reason before detection of distal DVT on the first scan were excluded from the present study.

Patients with distal DVTs were categorized into three groups as shown in Table 1: group 1, patients who received no

¹Department of General Medicine; ²Clinical Research Unit, Tan Tock Seng Hospital, Singapore

Correspondence: Dr Ashish Anil Sule, Department of General Medicine, Tan-Tock Seng Hospital, 11 Jalan Tan, Tock Seng, Singapore 308433.

Telephone 65-6357-7893 or 65-6357-7881, fax 65-6537-7588, e-mail ashishsule@yahoo.com

TABLE 1

Baseline characteristics in the 35 patients included in primary analysis

Characteristic	Group 1 (no treatment)	Group 2 (enoxaparin)	Group 3 (warfarin)	P
Patients, n	18	9	8	NA
Age, years (range)	71 (46–96)	66.44 (39–95)	59.88 (27–74)	0.206
Sex, male/female, n	14/4	7/2	5/3	0.686
Ethnicity				0.245
Chinese	16 (88.89)	7 (77.78)	5 (62.5)	
Indian	1 (5.56)	2 (22.22)	1 (12.5)	
Malay	1 (5.56)	0 (0)	2 (25)	
Immobility	7 (38.89)	1 (11.11)	2 (25)	0.311
Hypertension	15 (83.33)	5 (55.56)	6 (75)	0.297
DM	6 (33.33)	2 (22.22)	4 (50)	0.533
Hyperlipidemia	8 (44.44)	4 (44.44)	5 (62.5)	0.669
IHD	4 (22.22)	0 (0)	4 (50)	0.049
Obesity	0 (0)	1 (11.11)	0 (0)	0.226
Malignancy	2 (11.11)	2 (22.22)	1 (12.5)	0.729
Surgery				0.776
Hip	5 (44.44)	3 (33.33)	2 (25)	
Abdomen	0 (0)	1 (11.11)	1 (12.5)	
CNS	1 (5.56)	1 (11.11)	1 (12.5)	
Tobacco use	1 (5.56)	0 (0)	1 (12.5)	0.541
Alcohol use	1 (5.56)	0 (0)	0 (0)	0.615
Follow-up, months (range)	7.33 (1–18)	6.94 (1–24)	7 (3–18)	0.2062

Data presented as n (%) unless otherwise indicated. CNS Central nervous system; DM Diabetes mellitus; IHD Ischemic heart disease; NA Not applicable

treatment; group 2, patients who received subcutaneous enoxaparin (Clexane; Sanofi-aventis, France) 1 mg/kg twice a day for two weeks; and group 3, patients who received oral warfarin for three months with initial overlap of subcutaneous enoxaparin (Clexane) 1 mg/kg twice a day for three to five days until the prothrombin time international normalized ratio was between 2 and 3.

The mean follow-up period was 7.33 months, 6.94 months and seven months for groups 1, 2 and 3, respectively.

The primary outcome was measured by complete resolution of distal DVT on repeat duplex scan in the three groups. Repeated scans were taken at two weeks, one month, three months and six months, or on subsequent follow-up until the distal DVT resolved completely.

Secondary outcome measures assessed included complete improvement of symptoms, progression of thrombosis, or PE or death during the follow-up period. Symptoms assessed included leg pain, redness and swelling. Complete improvement of symptoms was defined as the resolution of all the symptoms on the last follow-up. If any of the symptoms persisted, then the patient was considered symptomatic. For categorical variables, the χ^2 or the Fisher's exact test (whichever was appropriate) was used to examine differences among the three treatment groups. ANOVA models were used to compare mean values (for instance, age and follow-up period) across the three treatment arms. The treatment and no treatment groups were also compared with mean variables using the independent Student's *t* test. Data analysis was performed in Stata version 9.2 (Stata Corp, USA) and all tests were performed at the 5% level of

TABLE 2

Primary outcome measures for resolution of distal deep venous thrombosis (DVT) in three groups

Distal DVT type	Total	Group 1 (no treatment)	Group 2 (enoxaparin)	Group 3 (warfarin)	P
Soleal vein, n	20	13	4	3	
Resolved, n (%)	10 (50)	5 (38.46)	3 (75)	2 (66.67)	0.363
Peroneal vein, n	16	7	6	3	
Resolved, n (%)	13 (81.25)	6 (85.71)	4 (66.67)	3 (100)	0.445
Posterior tibial, n	9	1	3	5	
Resolved, n (%)	8 (88.89)	1 (100)	3 (100)	4 (80)	0.638
Other calf vein, n	2	1	0	1	
Resolved, n (%)	2 (100)	1 (100)	0	1 (100)	NA

NA Not applicable

significance. The approval of the Domail Specific Review Board was obtained for the study.

RESULTS

Sixty-eight patients with distal DVT were seen during the period of study. However, 17 patients with PE, of whom two also had proximal DVT (in the iliac and common femoral veins) at the first presentation along with distal DVT, were excluded from the study. Thirteen of the 17 patients with PE had soleal vein thrombosis.

In total, 51 patients were included for analysis. A primary analysis was performed in only 35 patients, because 16 patients did not have a follow-up scan. All 51 patients had a secondary analysis.

Of the 35 patients included in primary analysis for resolution of distal DVT, there were 47 incidences of distal DVT; specifically, 20 soleal, 16 peroneal, nine posterior tibial and two gastrocnemius vein thromboses. Seventeen patients (25 distal DVTs) received anticoagulation treatment and 18 patients (22 distal DVTs) did not. Of the 17 treated patients, nine patients (13 distal DVT) received enoxaparin and eight patients (12 distal DVT) received warfarin.

Primary outcome measurements

Baseline characteristics were analyzed in the 35 patients in three groups, with follow-up scans for comparison of the primary outcome measurements in each group. There were no statistically significant differences among the three groups in the baseline characteristics age, sex, ethnicity, diabetes mellitus, hypertension, dyslipidemia, malignancy, history of surgery or DVT, obesity, family history of DVT and follow-up, except for ischemic heart disease ($P=0.049$) (Table 1).

There were no statistically significant differences in the outcomes for complete resolution of distal DVT (soleal, peroneal, posterior tibial, etc) among the three groups (Table 2 and Figure 1). There were also no statistically significant differences in outcomes of complete resolution of distal DVT between patients who did not receive anticoagulant treatment (group 1) and patients who were treated (groups 2 and 3) (Table 3).

Secondary analysis

All 51 patients were analyzed for symptom improvement. Data were available for 49 patients. All patients presented with symptomatic distal DVT. There was complete symptom resolution (no redness, swelling or pain on the last follow-up) in

Figure 1) Percentage of resolved veins by treatment group

24 of 28 patients (85.71%) in group 1, 10 of 11 patients (90.91%) in group 2, and 10 of 10 patients (100%) in group 3. However, the difference was statistically insignificant ($P=0.436$). There was one death in group 1 and no deaths in groups 2 and 3. The cause of death was not PE. There were no proximal extensions of distal DVT or episodes of PE in any of the patients.

DISCUSSION

During the past two decades, diagnosis of DVT has made considerable progress. Currently, there is no consensus on the natural history of distal DVT. Different authors have variably reported the rate of proximal extension of DVT. This has led to considerable debate over the treatment of distal DVT. The sensitivity and specificity of compression ultrasound for proximal DVT are high (97% and 98%, respectively). However, the same is not true for distal DVT. Studies have shown that while sensitivity of compression ultrasound in diagnosing distal DVT varies from 50% to 75%, the specificity varies from 90% to 95% (1,2). Although the embolic potential of proximal vein thrombosis is well recognized, distal clots appear to have a much lower embolic potential (4). Hence, the issue of rate of proximal extension of distal DVT assumes great importance as it largely determines the potential clinical relevance of distal DVT. The question of whether we should treat distal DVT has not been adequately answered. If treating distal DVT does not improve the outcome, then is there a need to search for a distal clot? Two issues – the necessity of searching for and treating distal DVT – have aroused intense debate among physicians. This has led to great differences in medical care among centres.

The literature describes various modalities of treatment for distal DVT, from no treatment to low molecular weight heparin and warfarin. Ohgi et al (5) examined 58 lower limbs using ultrasound in 29 patients suspected of having DVT distal to the popliteal vein. Venography revealed calf DVT in 33 limbs of 28 patients. Of the 28 patients, six had symptomatic PE. Thrombosis was found in the muscle veins in 18 limbs, the trunk veins in 11 limbs and both veins in four limbs. Isolated single vein thrombosis was found in the soleal vein in 14 limbs (42%), the posterior tibial vein in eight, the peroneal vein in two and the gastrocnemius vein in two. The overall percentage of soleal vein thrombi was 61%. All six patients with symptomatic PE had isolated soleal vein thromboses (5). Excluded from our study were 17 patients who had PE. Thirteen of the 17 patients had soleal vein thrombosis. It is difficult to ascertain

TABLE 3

Primary outcome measures for resolution of distal deep venous thrombosis (DVT) in group 1 (no anticoagulation) and groups 2 and 3 (anticoagulation)

Distal DVT type	Total	Group 1	Groups 2 and 3	P
Soleal vein, n	20	13	7	
Resolved, n (%)	10 (50)	5 (38.46)	5 (71.43)	0.160
Peroneal vein, n	16	7	9	
Resolved, n (%)	13 (81.25)	6 (85.71)	7 (77.78)	0.687
Posterior tibial, n	9	1	8	
Resolved, n (%)	8 (88.89)	1 (100)	7 (87.50)	0.708
Other calf vein, n	2	1	1	
Resolved, n (%)	2 (100)	1 (100)	1 (100)	NA

NA Not applicable

from the study whether soleal thrombosis is associated with PE or whether there was a proximal thrombus in all patients, with an embolization to the lungs. This association requires further study. However, when the PE patients were excluded in the beginning of our study, none of the isolated soleal thrombosis patients developed PE by follow-up. The mean follow-up periods were 7.33 months, 6.94 months and seven months for groups 1, 2 and 3, respectively.

Both the American College of Chest Physicians (6) and the Australasian Society of Thrombosis and Haemostasis (7) recommend treating distal DVT with anticoagulants. This was supported by a randomized study (8) of the usefulness of anticoagulation in distal DVT. It included 51 patients with symptomatic distal DVT diagnosed by phlebography. The recurrence rate at three months was 28% in patients not receiving anticoagulation (eight of 28) compared with 0% in those receiving anticoagulation. In the nontreated group, eight patients had a proximal extension of DVT and one experienced PE. However, 50% of these patients had previous thromboembolic events and were therefore at high risk of recurrence.

An open-label, randomized trial (9) compared a short oral anticoagulant course of six weeks with a long course of 12 weeks for isolated distal DVT. It was concluded, following isolated distal DVT, that six weeks of oral anticoagulation is sufficient.

To the contrary, discussions regarding the clinical significance of distal DVT have often been limited to the risk of PE, the investigation of which has yielded conflicting results. It does appear that the incidence of clinically significant PE with isolated distal DVT is lower than with proximal DVT and that most emboli that occur in this setting are small. However, whether this rate is trivial remains disputed. For example, the incidence of symptomatic PE among patients with asymptomatic distal DVT discovered in routine screening of postoperative patients has been reported to be as low as 0% to 2% (10-15). Screening asymptomatic high-risk patients for thrombi may be more difficult because asymptomatic thrombi may behave differently than symptomatic thrombi. Asymptomatic thrombi are often smaller, more often confined to the tibial veins and more frequently nonocclusive than symptomatic thrombi. Detection of these small thrombi by duplex ultrasound is also more difficult. The natural history of these thrombi may differ from symptomatic distal DVT, which is substantially less common than proximal venous thrombosis among symptomatic patients

(10-12). In our study, all the patients had symptomatic distal DVT with leg pain, swelling or redness.

In contrast, Lohr et al (16) observed PEs at presentation in 5% of patients and concluded that distal DVT was not a benign disorder. In our study, there were no patients who progressed to proximal DVT or PE. Our patients had isolated distal DVT because we excluded all patients with proximal DVT or PE.

The treatment of isolated distal DVT needs to be weighed against the bleeding risks of anticoagulation. Gorter (17) described an annual intracranial bleeding risk of 3.7% with anticoagulation after cerebral ischemia. Two prediction models have been developed and validated in outpatients treated with warfarin. Beyth et al (18) identified four independent risk factors for bleeding: age 65 years or older, history of gastrointestinal bleeding, history of stroke, and one or more of four specific comorbid conditions. This model was validated in another cohort of patients treated in another city; the cumulative incidence of major bleeding at 48 months was 53% in high-risk patients (three or four risk factors), 12% in middle-risk patients (one or two risk factors) and 3% in low-risk patients (no risk factors) (18). Kuijter et al (19) developed another prediction model based on age, sex and the presence of malignancy. In patients classified as high, middle or low risk, the frequencies of major bleeding were 7%, 4% and 1%, respectively, after three months of therapy.

Risk of bleeding from anticoagulation therapy is always a worry, particularly in the elderly population. This needs to be weighed against the risk of extension of distal DVT. However, the risk of progression of distal DVT is much lower compared with that of proximal DVT. In our study, none of the patients progressed to proximal DVT or PE. There was spontaneous resolution of distal DVT in those patients not treated with anticoagulation.

In 18 patients (22 incidences of distal DVT) not treated with anticoagulation, there was spontaneous resolution in 13 distal DVTs and the remaining nine distal DVTs did not progress over a mean period of 7.33 months.

Therefore, we would recommend that isolated, distal DVT be observed. We recommend the use of duplex scan at two weeks, one month and three months to observe for resolution or extension. If any progression of DVT on duplex scan or

worsening of symptoms occurs, we would recommend treatment.

Limitations of our study

1. This is a retrospective analysis but we only included patients with isolated, distal DVT.
2. The number of patients is limited but comparable with other studies. Moreover, distal DVT without proximal DVT or PE is not common. Our exclusion criteria were strict because we looked at only symptomatic, isolated distal DVT. We excluded patients who had proximal DVT or PE. Most studies in the literature report 20 to 50 patients for distal DVT. Moreover, data on isolated, distal DVT are very sparse.

Strengths of our study

1. Data on isolated, symptomatic, distal DVT with no history of PE or proximal DVT are very sparse.
2. We have excluded patients with proximal DVT or PE and past thromboembolic events, making the study results more robust.
3. The baseline characteristics in all three groups were similar. This also strengthens our analysis and provides more validity to the data.

We observed clinically significant results in our study. A meta-analysis of these groups of patients may be very useful because this would substantially increase the power of the study. It could also give us more useful information regarding treatment because the current recommendations for treatment in this group are controversial. We also recommend further evaluation of the group with soleal vein thrombosis and its association with PE.

CONCLUSION

Isolated distal DVT can be observed and may not need treatment. If leg symptoms worsen or there is progression of distal DVT on the follow-up scan we would recommend treatment with anticoagulation. The association of soleal thrombosis and PE needs to be studied further.

REFERENCES

1. Righini M, Paris S, Grégoire LG, Laroche JP, Perrier A, Bounameaux H. Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost* 2006;95:56-64.
2. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med* 1998;129:1044-9.
3. Anand SS, Wells PS, Hunt D, et al. Does this patient have deep vein thrombosis? *JAMA* 1998;279:1094-9.
4. Monreal M, Ruiz J, Olazabal A, et al. Deep venous thrombosis and the risk of pulmonary embolism. A systematic study. *Chest* 1992;102:677-81.
5. Ohgi S, Tachibana M, Ikebuchi M, Kanaoka Y, Maeda T, Mori T. Pulmonary embolism in patients with isolated soleal vein thrombosis. *Angiology* 1998;49:759-64.
6. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:401S-28S.
7. Gallus AS, Baker RI, Chong BH, et al. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 2000;172:600-5.
8. Lagerstedt CI, Olsson CG, Fagher BO, et al. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet* 1985;2:515-8.
9. Pinede L, Ninet J, Duhaut P, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001;103:2453-60.
10. Meissner MH, Caps MT, Bergelin RO, Manzo RA, Strandness DE. Early outcome after isolated calf vein thrombosis. *J Vasc Surg* 1997;26:749-56.
11. Hirsh J, Lensing AW. Natural history of minimal calf vein deep venous thrombosis. In: Bernstein E, ed. *Vascular Diagnosis*, 4th edn. St Louis: Mosby Year-Book, 1993:779-81.
12. Mattos MA, Londrey GL, et al. Color-flow duplex scanning for the surveillance and diagnosis of acute deep venous thrombosis. *J Vasc Surg* 1992;15:366-76.
13. Moreno-Cabral R, Kistner RL, Nordyke RA. Importance of calf vein thrombophlebitis. *Surgery* 1976;80:735-42.
14. Doouss TW. The clinical significance of venous thrombosis of the calf. *Br J Surg* 1976;63:377-8.

15. Solis MM, Ranval TJ, Nix ML, et al. Is anticoagulation indicated for asymptomatic postoperative calf vein thrombosis? *J Vasc Surg* 1992;16:414-9.
 16. Lohr JM, Kerr TM, Lutter KS, Cranley RD, Spirtoff K, Cranley JJ. Lower extremity calf thrombosis: To treat or not to treat? *J Vasc Surg* 1991;14:618-23.
 17. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: Patterns and risk factors. *Stroke Prevention In Reversible Ischemia Trial (SPIRIT)*. European Atrial Fibrillation Trial (EAFT) study groups. *Neurology* 1999;53:1319-27.
 18. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;105:91-9.
 19. Kuijter PM, Hutten BA, Prins MH, et al. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med* 1999;159:457-60.
-