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A retrospective analysis of patients treated for superficial vein thrombosis

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ABSTRACT

Introduction: The absolute risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) as well as extension and/or recurrence in superficial vein thrombosis (SVT) of the leg is considerable and underestimated. We retrospectively evaluated therapeutic management, thrombophilic risk factors and clinical outcome of SVT.

Methods: A database search was performed for consecutive patients with a suspected SVT of the lower extremities referred to our institution between 1 January 1999 and 31 December 2004. The primary outcome measure was pain reduction at follow-up. Secondary outcome measures were progression or recurrence of SVT in the leg and the occurrence of (a)symptomatic DVT or symptomatic PE at follow-up.

Results: In 73 patients follow-up information was present (3/76 non-evaluable patients). In 9/32 (28%) of the patients treated with carbasalate calcium, there was progression of SVT as assessed by ultrasonographic evaluation, compared with 3/11 (27%) in the low-molecular-weight heparin (LMWH) group and 3/6 (50%) in the no treatment group. DVT was diagnosed in 5/36 (14%) of the patients treated with carbasalate calcium compared with 1/13 (1%) in the LMWH and 1/3 (33%) in the other treatment groups at follow-up. Furthermore, 34 were tested for thrombophilic defects, 27 of whom had one or more thrombophilic defect.

Conclusion: The results of our study show that SVT may be prone to venous thromboembolism and therefore needs to be treated or carefully followed up.

KEYWORDS

Superficial phlebitis, superficial thrombophlebitis, superficial vein thrombosis, venous thromboembolism, venous thrombosis

INTRODUCTION

The incidence of superficial vein thrombosis (SVT) of the leg has never been adequately assessed, but is estimated to be higher than that of deep vein thrombosis (DVT), which has an incidence of 1 per 1000 inhabitants per year.[1-3] The fact that the incidence is not known can be partially explained by the different terms used for this disease: superficial phlebitis, superficial thrombophlebitis or superficial vein thrombosis. In general 'superficial phlebitis' refers to the clinical findings of inflammation such as pain, tenderness and/or erythema along the affected superficial vein, often palpable as a cord. The term 'superficial vein thrombosis' is used when a thrombus is found by diagnostic testing such as compression ultrasonography (CUS) or phlebography.[4,5]

The absolute risk of DVT or pulmonary embolism (PE) (called venous thromboembolism, VTE) and extension and/or recurrence in SVT is not well known and likely underestimated.[6] Until recently SVT was considered a benign disease, but several studies have suggested otherwise,[7-11] although the association between SVT and VTE has been debated.[12] Because of its location, SVT of the vena saphena magna or the saphenous-femoral junction is thought to have the highest risk of progressing to a deep venous thrombosis and/or embolisation to the pulmonary arteries.[13,14]

Predisposing risk factors for SVT are very similar to those for VTE. These include postoperative states, pregnancy, active malignancies, autoimmune diseases, use of oral contraceptives, previous venous thromboembolism and varicose veins.[15-19] In addition, the factor V Leiden (G1691A) and prothrombin mutation (20210A) as well as deficiencies of the natural anticoagulant proteins C and S are also diagnosed more often in patients with SVT than in healthy individuals, which further strengthens the hypothesis that SVT and VTE have a comparable aetiology.[20-23]

To date patients are often either not treated or receive creams, elastic stockings or non-steroidal anti-inflammatory agents (NSAIDs). The association of VTE with SVT has raised the question whether this conservative management, mainly aimed to improve the painful symptoms, is sufficient. Therefore, several other therapies have been proposed, ranging from surgical ligation or stripping of the affected veins to full-dose anticoagulant therapy.[24-28] After reviewing the available literature on treatment of SVT, active treatment with NSAIDs or LMWH (prophylactically or therapeutically) appears to reduce the incidence of SVT extension and/or recurrence compared with placebo.[6] However, during a longer follow-up this benefit was lost. There is not enough evidence to support surgical intervention or topical treatment based on the literature currently available.[29]

This retrospective follow-up study was performed to evaluate therapeutic management, thrombophilic risk factors and clinical outcome of SVT in our clinic over the past six years. Furthermore, we were interested in the trend of therapeutic management over time in our clinic, since the publication of several therapeutic management studies of SVT. We assessed pain reduction, extension and/or recurrence of SVT in the lower extremities and progression to DVT/PE after treatment.

METHODS

Data collection

The Department of Vascular Medicine of the Academic Medical Center in Amsterdam, the Netherlands, offers a daily diagnostic service for patients who are suspected of having DVT. The ultrasound technicians are specialised in the diagnosis of venous thrombotic disease. Patients visiting this diagnostic service are referred by their general practitioner or are hospitalised for other conditions. Diagnoses of all patients visiting the clinic have been prospectively collected since 1997. In this electronic database a search was performed for patients diagnosed with an SVT of the lower extremities between 1 January 1999 and 31 December 2004. The medical files of all patients were checked for date of onset of symptoms, treatment taken before presentation, date of diagnosis, risk factors for VTE, diagnostic tests used, localisation of the SVT, type of treatment and follow-up information (both history and ultrasound data). Pain and ultrasonographic evaluations were interpreted and scored by two investigators (IW, MH) independently. Extension of an SVT was considered present if the thrombus had extended in length or diameter.

Furthermore, medical files were checked for findings of thrombophilic risk factors (factor V Leiden, prothrombin mutation, deficiency of protein C/S/antithrombin, lupus anticoagulans, anticardiolipin antibodies and elevated levels of factor VIII) and DVT or PE at follow-up. An effort was made to contact patients if follow-up information was missing. Patients identified as having concomitant DVT at the time of diagnosis of SVT were not included. Other exclusion criteria were anticoagulant treatment (except when initiated for the present episode of SVT by their general practitioner), surgical intervention (stripping, ligation or crossectomy) or SVT at another location than the legs.

Outcome measures

The primary outcome measure was pain reduction at follow-up after a minimum of six days to six months. Secondary outcome measures were progression or recurrence of SVT in the leg and the occurrence of (a) symptomatic DVT or symptomatic PE at follow-up after a minimum of six days to six months.

RESULTS

Database search results

The database search for patients with SVT resulted in 131 hits. Of these, 55 patients were excluded from the study for the following reasons: because no SVT was diagnosed (40), SVT was localised in the arm (1), co-existent PE (3) or DVT (4), patients were using anticoagulant treatment for other indications (2), had undergone stripping of the vena saphena magna and/or parva (4), and the medical file could not be retrieved (1). Follow-up information for symptoms and ultrasonographic evaluation was missing in three patients: two women (48 years of age, oral contraceptive use, history of SVT and factor V Leiden and 61 years, no information) and a man (25 years, sickle cell anaemia, a history of venous thrombosis, recent surgery and the prothrombin mutation).

Diagnosis of SVT

The baseline characteristics of the 73 patients are detailed in *table 1*. Patients in whom SVT was diagnosed were relatively young (median 54 years) and there was no difference in sex (47% male). The diagnosis of SVT was confirmed by compression ultrasonography on the day of presentation in 72 of the cases. In one patient the diagnosis of SVT was made by clinical symptoms only at the first visit, but SVT was objectively documented at follow-up. Of the 73 patients SVT was located in the vena saphena magna, the vena saphena parva and in both veins in 38, 20 and 12, respectively. Two of the 73 patients had SVT in a superficial calf vein, in one the location was not described.

Risk factors for SVT: inherited and acquired thrombophilic defects

Table 1 details the risk factors for SVT. In this population, 14 of a total of 57 (21%) patients had a history of VTE. Immobilisation, trauma and surgery preceded a relatively

Table 1. *Baseline characteristics*

	Patients (n=73)	
Characteristic	**n**	**%**
Age (median (years) ± SD)	54 ± 19	
Male gender	34	47
Interval between symptom onset and diagnosis:		
• Median (days)	7	
• Range (days)	1-160	
• ≤14 days	60	86
• Date of onset missing	3	4
Diagnosis confirmed:		
• Complete ultrasound	72	99
• On clinical grounds	1	1
Location superficial vein thrombosis:		
• Vena saphena magna (VSM)	38	52
• Vena saphena parva (VSP)	20	27
• VSM and VSP	12	16
• Superficial calf veins	2	3
• Unclear	1	1
Risk factors (present/absent)	**n/N***	**%**
History of venous thromboembolism	14/43	33
Immobilisation in the last 3 months	5/45	11
Trauma in the last 3 months	6/45	13
Surgery in the last 3 months	4/49	8
Malignancy	3/46	7
Family history of venous thromboembolism	11/36	31
Female risk factors:		
• Oral conceptive use or HRT	9/17	50
• Puerperium (<6 weeks)	4/22	18
• Pregnancy	4/22	18

*Number of patients with risk factors described is variable; HRT = hormonal replacement therapy.

low number of SVTs, i.e. in 5/50 (10%), 6/51 (11%) and 4/53 (8%) patients, respectively. Hormone replacement therapy or oral contraceptives were taken by 9/26 (35%) women with SVT, 4/26 (15%) women were pregnant and 4/26 (15%) were in their puerperium period at the time of diagnosis.

Thirty-four of the 73 patients (47%) were tested for one or more thrombophilic abnormalities. Of the 34 tested patients, 27 (79%) had one or more thrombophilic defect. In 9/31 (29%) of the patients the factor V Leiden mutation was found (1 homozygous). Furthermore, 3/32 (9%) of the patients had a prothrombin mutation: heterozygous (2) and homozygous (1). Two out of 31 patients (6%) had a protein C deficiency and 1/31 patient (0.3%) a protein S deficiency. Elevated factor VIII levels were frequently found (based on a single measurement in the majority of the cases), i.e. 16/25 (64%) patients tested.

Treatment after the established diagnosis of SVT

Treatment prior to referral

In 12 of the 73 cases the patient had been treated before referral, with antibiotics (6), vitamin K antagonists (2), elastic compression stockings and carbasalate calcium (1), carbasalate calcium alone (1), prophylactic dose of low-molecular-weight heparin in a hospitalised patient (1) and hiroid cream (1).

Following the established diagnosis of SVT, 40 of the 73 (55%) patients received treatment with carbasalate calcium (500 to 600 mg three times daily) for a median duration of ten days (range 3 to 21; one missing value) (*table 3*). Two of these patients were also given an elastic compression stocking. Fifteen patients (21%) were treated with a therapeutic dose of low-molecular-weight heparin for a median duration of 14 days (range 7 to 64), two patients also got a prescription for an elastic compression stocking (ECS), one of whom also received antibiotics. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed to three patients (4%) as were vitamin K antagonists. In one patient (1%) low-molecular-weight heparin was combined with carbasalate calcium for treatment of the SVT. Six patients (8%) received no medical treatment or compression stockings.

Carbasalate calcium was predominantly given as treatment for SVT between 1999 and 2003. In 2004, however, more patients were treated with low-molecular-weight heparin.

Clinical outcome

Reduction of symptoms at follow-up

Most patients (n=60, 87%) were referred within two weeks after the onset of symptoms (median 7 days; range 1 to 160; three missing). Twenty-three patients out of 36 (64%) treated with carbasalate calcium compared with 12/12 (100%) in the low-molecular-weight heparin group and 1/4 (25%) in the no treatment group reported reduction in pain at follow-up (*table 2*). Another two patients had a reduction in symptoms after treatment with low-molecular-weight heparin, which was prescribed when pain persisted after an initial treatment with carbasalate calcium and no treatment. Increase in pain was observed in 5/36 (14%) of the patients treated with carbasalate calcium. No patients had increased pain after treatment with low-molecular-weight heparin and 1/4 (25%) after not being treated. Data on symptoms were missing in 11/73 (15%) of the patients, four of whom had an SVT progression or recurrence and two had a DVT at follow-up.

Progression and/or recurrence of SVT at follow-up

Ultrasonographic evaluation of SVT at follow-up was available in 56/73 patients (77%) (median 11 days after diagnosis of SVT; range 5 to 129). In 9/32 (28%) of the patients treated with carbasalate calcium there was progression and/or recurrence of SVT as assessed by ultrasonographic evaluation, compared with 3/11 (27%) in the low-molecular-weight heparin and 3/6 (50%) in the no treatment group (*table 2*). Nine of 17 patients with missing results on ultrasonographic evaluation of SVT reported pain reduction

Table 2. *Symptoms at follow-up after treatment with carbasalate calcium, nadroparin or other treatments*

	Pain			
Treatment (n*)	**Increase (n, %)**	**Same (n, %)**	**Decrease (n, %)**	**Unknown (n)**
Carbasalate calcium (36)	5, 14	8, 22	23, 64	4
Nadroparin (12)	0, -	0, -	12, 100	3
No treatment (4)	1, 25	2, 50	1, 25	2
Vitamin K antagonists (3)	0, -	0, -	3, 100	0
NSAIDs (3)	1, 33	0, -	2, 67	0
Nadroparin + carbasalate calcium (1)	0, -	0, -	1, 100	0
Other (3)	1, 33	0, -	2, 67	2

*Missing follow-up information (see column 'unknown') was not included in the total number of treated patients.

Table 3. *Superficial venous thrombosis and deep venous thrombosis at first follow-up after treatment with carbasalate calcium, nadroparin or other treatments*

	Results compression ultrasonography					
Treatment (n*)	**Extension and/or recurrence of superficial venous thrombosis**			**Deep venous thrombosis**		
	Yes (n, %)	**No (n, %)**	**Unknown (n)**	**Yes (n, %)**	**No (n, %)**	**Unknown (n)**
Carbasalate calcium (32 *vs* 36)	9, 28	23, 72	8	5, 14	31, 86	4
Nadroparin (11 *vs* 13)	3, 27	8, 73	4	1, 8	12, 92	2
No treatment (6)	3, 50	3, 50	0	0, -	6, 100	0
Non-steroidal anti-inflammatory drugs (3)	1, 33	2, 67	0	0, -	3, 100	0
Vitamin K antagonists (2 *vs* 3)	0, -	2, 100	1	0, -	3, 100	0
Nadroparin + carbasalate calcium (1)	1, 100	0, -	0	0, -	1, 100	0
Other (1 *vs* 3)	0, -	1, 100	4	1†, 33	2, 67	2

*Missing follow-up information (see column 'unknown') was not included in the total number of treated patients. †Patient was treated with hiroid cream

at follow-up, two patients had a DVT and six patients did not have a symptomatic VTE at follow-up. Eight of 17 patients had no ultrasonographic evaluation of SVT and DVT at follow-up, five had a reduction in symptoms at follow-up and seven did not have a symptomatic VTE at follow-up.

Occurrence of DVT at follow-up

Ultrasonographic evaluation of DVT at follow-up was available in 65/73 (89%) of the patients (median 10 days after diagnosis of SVT; range 3 to 129). Two patients developed a DVT within one week (day 3 and 5). DVT was diagnosed in 5/36 (14%) of the patients treated with carbasalate calcium compared with 1/13 (8%) in the low-molecular-weight heparin and 1/3 (33%) in the other treatment group at follow-up (*table 3*). As mentioned above, of the eight patients without ultrasonographic evaluation, five had a reduction in symptoms at follow-up and seven did not have symptomatic VTE at follow-up.

DISCUSSION AND CONCLUSION

In our centre, SVT was traditionally treated with carbasalate calcium, because of its anti-inflammatory and pain-reducing properties. In 2004, an increasing number of patients with SVT were treated with low-molecular-weight heparin, which was probably due to the publication of randomised trials on treatment and natural history of SVT, showing that active treatment with NSAIDs or LMWH may reduce the incidence of progression and/or recurrence of SVT.[27,30] Another reason for abandoning treatment with carbasalate calcium was the lack of evidence for the efficacy of this type of treatment for SVT.

Our findings indicate that SVT has similar inherited and acquired risk factors to those known for VTE, as has been described by others.[19,20,23]

Nevertheless, SVT progressed to DVT in 7/65 (11%) of the cases, which confirms that SVT is not a benign disease.[6,10,31] Interestingly, pain reduction at follow-up was accomplished more often in patients treated with low-molecular-weight heparin compared with treatment with carbasalate calcium. SVT progression and/or recurrence was comparable in both the carbasalate calcium and low-molecular-weight heparin group, but higher in patients who were not treated at all. DVT occurred in one patient treated with low-molecular-weight heparin compared with five patients in the carbasalate calcium group. None of the patients who had been managed conservatively developed DVT. These findings should be interpreted with caution, since the interventions were not prescribed in a randomised fashion,

and the observations are likely to be biased by selective treatment of patients with more severe symptoms.

Risk factors for VTE are also found in patients with SVT, which strengthens the concept that SVT and VTE share the same aetiology. The results of our study show that patients with SVT may be prone to VTE and therefore need to be treated or carefully followed. Furthermore, these results stress the need for large (multi-centre) trials for the treatment of SVT.

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