Thrombosis Research 136 (2015) 1116–1119

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Seasonal variation in the superficial vein thrombosis frequency

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form 22 September 2015
Accepted 4 October 2015
Available online 8 October 2015

Keywords:
Thrombophlebitis
Incidence
Seasons
Adult
Chronobiology phenomena

ABSTRACT

Introduction: A seasonal variation of venous thromboembolic disease frequency is subject to discussion, and has been recently suggested for superficial vein thrombosis (SVT) in a small retrospective study. Our aim was to search for a seasonal variation of SVT frequency according to the data of larger studies.
Materials and methods: We analyzed the data of three French prospective multicenter studies with different designs which have included patients with SVT (STENOX, POST, and STEPH studies). Seasonal variation of SVT frequency was evaluated by comparing the observed seasonal frequency of SVT to a theoretical frequency of 25% for each season.
Results: The analysis included 1395 patients and 4.75 seasonal cycles. The difference to a theoretical frequency of 25% was statistically significant in one study (POST, $p = 0.044$). The higher risk difference was −6.1% (95% CI −11.7–−0.5) in summer in STENOX, +7.1% (95% CI +2.7–+11.5) in winter in POST and 4.2% (95% CI −5.2–+13.7) in spring in STEPH, corresponding to a relative risk of 0.80, 1.40 and 1.20, respectively.
Conclusions: A seasonal variation was found in only one study which has the weakest methodology to warrant completeness. Variation pattern was different in each study. If this variation exists, it would probably be too low to have clinical consequences.

1. Introduction

The knowledge of diseases prevalence/frequency seasonal variations may incite health professionals to vigilance during peak periods, induce human resources adjustment during these periods, and overall, give keys to understand the underlying pathophysiological mechanisms.

Seasonal variation of venous thromboembolism (VTE) frequency is debated [1–4]. Several studies suggested that prevalence of deep vein thrombosis (DVT) and pulmonary embolism (PE) is higher in the winter and lower in the summer. This could be explained by the increased levels of coagulation factors and the increased frequency of common transient infections associated with cold temperatures [5–11]. However, if it does exist, this difference has been estimated to be around 2% and does not seem to be clinically significant [2,4].

Considered as benign for a while, superficial vein thrombosis (SVT) became a new point of interest in the field of VTE. Recent studies demonstrated its potential severity and opened new ways of therapeutic management [12–18].

To our knowledge, only one study investigated circannual variation of SVT frequency [19]. Surprisingly, the SVT frequency was higher during the summer. However, the 123 patients of this study were enrolled by a unique emergency department, potentially exposed to a different population during the summer. Moreover SVT were not systematically confirmed by ultrasonography, and frequencies were calculated with absolute numbers without adjustment on a population denominator. As this kind of results may be influenced by the design of the study, we aim to search for a seasonal variation of SVT frequency in large-scale studies using different designs.

2. Materials and methods

2.1. Study type

We conducted a post-hoc analysis of individual data of three large French prospective studies on SVT; the STENOX study, the POST study

Abbreviations: SVT, superficial vein thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism.

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http://dx.doi.org/10.1016/j.thromres.2015.10.007
0049-3848/

and the STEPH study. The STENOX study was a national randomized controlled trial comparing a treatment by subcutaneous enoxaparin sodium 4000 IU, subcutaneous enoxaparin sodium 150 IU/kg, oral tenoxicam 20 mg per day or placebo once daily for 8 to 12 days. Four hundred and twenty seven patients have been enrolled between April 1996 and April 1997 and between September 1997 and December 1998 [14]. The POST study was a national prospective epidemiological study whose main objective was to assess the incidence of thromboembolic complications of SVT at 3 months. Eight hundred and forty-four patients have been included between March 2005 and October 2006 [12]. The STEPH study was a one-year prospective community-based incidence study performed in a well-defined geographic area of 265,687 adult residents. One hundred and seventy-one patients with SVT have been inventoried between November 14, 2011 and November 13, 2012 [18].

2.2. Patients recruitment

The STENOX study comprised hospitalized or non-hospitalized patients older than 18 years, weighing 45 to 110 kg, with acute symptomatic lower-limb SVT at least 5 cm long on duplex ultrasonography. Patients were not include if they had another thromboembolic event, a fragile background (pregnancy, breastfeeding, women of childbearing age not using contraception, thrombophilia, uncontrolled arterial hypertension, peptic ulcer, bacterial endocarditis, recent stroke, other conditions favoring hemorrhage, history of hypersensitivity to heparins, history of heparin-induced thrombocytopenia, hypersensitivity to paracetamol or nonsteroidal anti-inflammatory agents, serum creatinine concentration above 1.81 mg/dL, platelet count below 100 G/L, prothrombin ratio below 60%, or contraindication to elastic bandages or support stockings), if they required a specific treatment (anticoagulant or surgery), or if they had started a treatment for more than 48 h.

The POST study enrolled patients aged 18 years or older, with a symptomatic lower-limb SVT more than 5 cm of length on duplex ultrasonography. Patients were not included if they underwent a recent surgery, if SVT occurred after recent sclerotherapy or if the patient cannot be follow up for 3 months. All office- and hospital-based vascular physicians who were registered with 2 specialty societies, the Société Française de Médecine Vasculaire or the Société Française de Phlébologie, were invited to enroll patients in the study.

The STEPH study included, during one year, all ≥18-year old hospitalized or non-hospitalized inhabitants of the study-area having an ultrasonography-confirmed SVT. Patients were identified by primary, secondary and tertiary care physicians from both private and public practices located in the study area.

2.3. Cases ascertainment

In the three studies, all SVT cases were objectively confirmed by a duplex ultrasonography and reviewed blindly by an independent clinical adjudication committee.

2.4. Statistical analysis

Frequency of SVT was calculated for each season. Seasons were defined as followed: winter from December 21 to March 20, spring from March 21 to June 20, summer from June 21 to September 21 and autumn from September 22 to December 20. Seasonal rates of SVT were compared, by the chi-square adjustment test, to a theoretical proportion of 25% of the events in each season. Qualitative data were reported as numbers and percentages. Quantitative data were reported as median and interquartile ranges. The significance level has been set at $p < 0.05$, with bilateral setting. SAS-Windows® version 9.3 (SAS Institute, Cary, North Carolina) was used to analyze and process all data. The peak-to-low ratios were used in univariate analyses of seasonality and were performed using Episheet [20,21].

3. Results

Clinical characteristics of the 1395 patients included in the three studies are displayed in Table 1. For each study, the number of SVT cases included by season is presented in Table 2.

The time to peak was February 11th in the STENOX study, August 13th in the POST study and March 24th in the STEPH study. In all three studies, there was a graphical trend toward a lower frequency of SVT in summer (Fig. 1). Compared with a theoretical distribution of 25% events for each season, the difference was statistically significant only in the POST study ($p = 0.536$ in STENOX, 0.044 in POST, and 0.412 in STEPH). The higher risk difference to 25% was −6.1% (95% CI −11.7–−0.5) in summer in STENOX, 7.1% (95% CI +2.7–+11.5) in winter in POST and 4.2% (95% CI −5.2–+13.7) in spring in STEPH, corresponding to a relative risk of 25 / 31.1 = 0.80, 25 / 17.9 = 1.40 and 25 / 20.8 = 1.20, respectively. The peak-to-low ratio was 1.14[1.00–1.72] in the STENOX study, 1.01[1.00–1.29] in the POST study and 1.16[1.00–1.78] in the STEPH study.

4. Discussion

Our study found a significant seasonal variation in the SVT frequency only in one of the three studies. Variation pattern was also different in each study and their peak-to-low ratios were all below 1.2.

To our knowledge, this is the first study assessing seasonal variation of SVT frequency with a such statistical power: 171 to 805 patients have been included depending on the studies, and a total of 4.75 seasonal cycles were analyzed, whereas Kakkos et al. based their analysis on only 123 patients and 2 seasonal cycles [19]. Methodological diversity of the studies allows discussion of our results, based on the potential bias of each study. First, the inclusion process in the STENOX and the POST studies could have been influenced by confusing factors, such as newsletters or investigators' meetings. Secondly, the STENOX study did not include patients presenting a SVT initially associated with DVT or PE. Finally, due to its interventional design, the STENOX study presented several exclusion criteria and its results may not reflect the frequency of SVT in an at-risk population. On the other hand, the STEPH study was designed to achieve completeness as much as possible. All the primary,

Table 1
Patients and SVT characteristics.

	STENOX	POST	STEPH	Total
SVT, n (%)	419 (100.0)	805 (100.0)	171 (100.0)	1395 (100.0)
Women, n (%)	265 (63.2)	521 (64.7)	111 (64.9)	897 (64.3)
Age (median), (IQR)	65 (53–73)	65 (50–74)	68 (56–79)	65 (52–74)
BMI > 30 kg/m^2, n (%)	89 (21.2)	230 (28.7)	37 (25.3)	356 (26.0)
Personal history of thromboembolism, n (%)	61 (14.6)	172 (22.0)	33 (24.3)	266 (19.9)
SVT at or above knee, n (%)	–	242 (46.3)	57 (33.3)	299 (48.8)
Associated DVT and/or PE, n (%)	–	204 (25.3)	45 (26.3)	249 (25.5)

IQR: interquartile range; BMI: body mass index; SVT: superficial vein thrombosis; DVT: deep vein thrombosis; PE: pulmonary embolism.