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Full Length Article

A multicenter prospective study of risk factors and treatment of unusual site thrombosis☆

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ABSTRACT

Unusual site deep vein thrombosis (USDVT) is an uncommon form of venous thromboembolism (VTE) with heterogeneity in pathophysiology and clinical features. While the need for anticoagulation treatment is generally accepted, there is little data on optimal USDVT treatment. The TRUST study aimed to characterize the epidemiology, treatment and outcomes of USDVT. From 2008 to 2012, 152 patients were prospectively enrolled at 4 Canadian centers. After baseline, patients were followed at 6, 12 and 24 months. There were 97 (64%) cases of splanchnic, 33 (22%) cerebral, 14 (9%) jugular, 6 (4%) ovarian and 2 (1%) renal vein thrombosis. Mean age was 52.9 years and 113 (74%) cases were symptomatic. Of 72 (47%) patients tested as part of clinical care, 22 (31%) were diagnosed with new thrombophilia. Of 138 patients evaluated in follow-up, 66 (48%) completed at least 6 months of anticoagulation. Estrogen exposure or inflammatory conditions preceding USDVT were commonly associated with treatment discontinuation before 6 months, while previous VTE was associated with continuing anticoagulation beyond 6 months. During follow-up, there were 22 (16%) deaths (20 from cancer), 4 (3%) cases of recurrent VTE and no fatal bleeding events. Despite half of USDVT patients receiving <6 months of anticoagulation, the rate of VTE recurrence was low and anticoagulant treatment appears safe. Thrombophilia testing was common and thrombophilia prevalence was high. Further research is needed to determine the optimal investigation and management of USDVT.

1. Introduction

Venous thromboembolism (VTE) is a common medical condition that incurs significant morbidity and mortality: the annual estimated incidence rate ranges from 104 to 183 per 100,000 person-years and [1]. The most common sites for VTE are deep vein thrombosis (DVT) of the limbs and pulmonary embolism (PE), with an incidence of approximately 0.78 and 0.45 per 1000 person-years, respectively [2]. Unusual site deep vein thrombosis (USDVT) refers to a less common and more heterogeneous manifestation of VTE that can occur in a variety of deep veins, including the mesenteric, portal, splenic, ovarian, jugular or cerebral veins [3].

Depending on the site affected, there exists significant heterogeneity in the pathophysiology, clinical features and prognosis of USDVT. For example, some USDVT are strongly associated with local precipitating factors such as cirrhosis in the case of portal vein thrombosis (PVT), and central venous catheters (CVC) in the case of jugular vein thrombosis [4]. Other USDVT have been more strongly associated with systemic precipitants, such as estrogen exposure for cerebral vein thrombosis and Janus kinase 2 (JAK2) mutation for splanchnic vein thrombosis, even in the absence of a myeloproliferative disorder [5,6]. In recent

Abbreviations: USDVT, unusual site deep vein thrombosis; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis; CVC, central venous catheter; JAK2, Janus kinase 2; CT, computed tomography; MR, magnetic resonance; UFH, unfractionated heparin; LWMH, low molecular weight heparin; VKA, vitamin K antagonist; INR, international normalized ratio; ACCP, American College of Chest Physicians.

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years, it has been reported that different acquired and inherited thrombophilic states may predispose to different sites of USDVT. For example, the factor V Leiden is associated with cerebral vein thrombosis while the prothrombin G20210A mutation is associated with PVT, but not Budd-Chiari syndrome [7,8].

Due to its less frequent incidence than limb DVT and PE, most information on USDVT in the literature has been derived from case reports or case series. The necessity of anticoagulation in the treatment of USDVT is generally accepted, but there is a paucity of data regarding the optimal duration or safety of such treatment [9]. Thus, USDVT continues to pose a significant clinical dilemma. We report the results of a prospective, multicentre observational study on the epidemiology, treatment and outcomes associated with USDVT.

2. Materials and methods

2.1. Study design and patients

The TRUST (Treatment and Risk Factors for Unusual Site Thrombosis) Study is a prospective multicenter observational study of patients with USDVT, defined as thrombus within the splenic, portal, mesenteric, hepatic, renal, ovarian, jugular or cerebral veins. USDVT had to be objectively diagnosed within the previous six months using imaging modalities that included ultrasound, computed tomography (CT), magnetic resonance (MR), or venography. Patients were eligible regardless of whether the index USDVT was a first or recurrent VTE, and whether the event was symptomatic or asymptomatic. Patients were excluded from participation if any of the following criteria were present: geographic barrier to attending follow-up visits; unable to understand or speak English or French (language barrier); or unable or unwilling to provide signed informed consent. The institutional review board or ethics committee of each institution approved the study protocol, and each patient provided written informed consent before enrolment.

2.2. Study procedures

A standardized treatment was recommended in the study protocol, consisting of an initial 5–7 day course of unfractionated heparin (UFH) or low molecular weight heparin (LMWH), followed by six months of therapeutic anticoagulation either with LMWH monotherapy or vitamin K antagonists (VKA), with an INR target of 2.5.

At the baseline visit, data were recorded on sex, age, site of USDVT, and potential VTE risk factors (e.g. medical or surgical hospitalization within 3 months of diagnosis, immobilization, cancer, family history of VTE, use of estrogenic medications). After enrollment, patients attended follow-up visits at six months, 1 year and 2 years. At each follow-up visit, information was collected using a standardized case report form on vital status (alive/dead; cause of death), objectively-confirmed recurrent VTE events, residual symptoms of USDVT, thrombophilia testing results if available, and whether anticoagulant treatment was ongoing or had been stopped. In the case of recurrence on anticoagulation during follow-up, we documented the most recent INR.

2.3. Statistical analysis

Demographic and clinical data were summarized using means and standard deviations, or medians and interquartile ranges, for continuous variables, and using numbers and percentages for categorical variables. Summarized data are presented separately for each USDVT site where possible based on the number of cases. Baseline characteristics were compared among patient subgroups, according to the therapeutic strategies, using chi-square or Fisher exact test for dichotomous variables, and *t*-test for continuous variables.

3. Results

A total of 152 patients were recruited between May 2008 and October 2012 at four Canadian tertiary care centers (Jewish General Hospital, Montreal, Quebec; Queen Elizabeth Health Center, Halifax, Nova Scotia; Ottawa Hospital, Ottawa, Ontario; St. Joseph's Health Center, London, Ontario). Median time from diagnosis to study entry was 15.5 days, and 19 patients (13%) were recruited 100 days or more following initial diagnosis of USDVT. There were 97 (64%) cases of splanchnic, 33 (22%) cerebral, 14 (9%) jugular, 6 (4%) ovarian and 2 (1%) renal vein thrombosis (Fig. 1).

Baseline characteristics of the study patients are described in Table 1. Mean age was 52.9 ± 15.4 years. There was a slight female preponderance, with 82 (53%) females and 70 (46%) males overall, while for jugular vein thrombosis, there were more male patients (64%) than female (36%). Most cases were symptomatic (74%) and the remainder were diagnosed incidentally. In particular, 31 of 33 cases (94%) of cerebral vein thrombosis were symptomatic at presentation.

Recent hospitalization was the most common risk factor for USDVT: 62 patients (41%) were admitted to hospital within three months preceding the USDVT diagnosis. It was also the most common risk factor for ovarian, jugular and splanchnic vein thrombosis. A central venous catheter was observed in 9 patients (64%) with jugular venous thrombosis. Of these patients, four had a concomitant malignancy, of whom three were receiving chemotherapy via their central venous catheter (CVC). Most cerebral vein thrombosis appeared unprovoked, although estrogen exposure was a common underlying risk factor in 53% of women with cerebral vein thrombosis. Three (2%) patients were known to have a hypercoagulable state prior to the diagnosis of USDVT, and a history of prior VTE was reported in 19 (13%) patients with USDVT.

Baseline characteristics of the 97 patients with splanchnic vein thrombosis, according to involved vein(s), are shown in Table 2. Most cases (59%) involved the portal vein. The majority of cases were symptomatic, ranging from 63 to 77% of cases, and recent hospitalization was the most common risk factor for mesenteric (50%), portal (47%) and "other" splanchnic vein thrombosis (70%).

Initial treatment of USDVT is described in Table 3. The most commonly used anticoagulation treatment for most USDVT was LMWH bridged to warfarin therapy. The exception was jugular vein thrombosis, which was treated with LMWH alone in 64% of patients. Nine (6%) of patients received either monotherapy with aspirin or warfarin with no heparin bridge, and three (2%) patients did not receive any anticoagulation therapy.

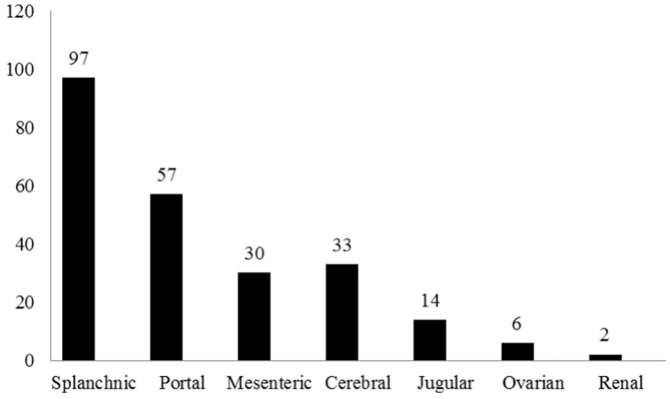

Fig. 1. Number of cases of USDVT by thrombosis site (n = 152). USDVT unusual site deep vein thrombosis. * Splanchnic vein thrombosis included: isolated portal vein (57), isolated mesenteric vein (30), isolated splenic vein (1), and thrombosis in multiple intra-abdominal sites (9).