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Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review

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KEYWORDS

Upper extremity deep vein thrombosis (UEDVT)
Central venous catheter (CVC)
Recurrent venous thromboembolism (VTE)
Mortality
Bleeding complications
Neoplasms
Anticoagulant therapy

ABSTRACT

Background: The incidence of upper extremity deep vein thrombosis (UEDVT) is increasing. Information on the clinical course of UEDVT is scarce, especially in cancer patients.
Aim: To summarize the clinical evidence regarding long-term clinical outcomes of UEDVT, in terms of recurrent venous thromboembolism (VTE), mortality, and anticoagulant-related bleeding, in patients with or without concomitant cancer.
Methods: A systematic search of the literature was conducted in MEDLINE, EMBASE and BIOSIS Previews. Incidence rates for all outcome variables were calculated.
Results: In total, 45 studies comprising 4580 patients were included. No randomized controlled trials were identified. In most studies, patients were treated solely with anticoagulants. Among the prospective studies, the incidences of recurrent VTE and bleeding complications averaged 5.1% and 3.1% respectively, during 3 to 59 months of follow-up. In the retrospective studies these figures were 9.8% and 6.7% respectively. Among the prospective studies, the mortality rate was 24% after one year. In the retrospective studies this rate was 35%. Cancer patients were found to have a 2- to 3-fold higher risk of recurrent VTE, an 8-fold increased risk of mortality, and a 4-fold increased risk of bleeding during anticoagulant therapy, compared to non-cancer patients.
Conclusions: Studies were very heterogeneous in terms of study design, study populations and treatment approaches. Follow-up durations varied greatly, hampering combined analyses of average incidence rates. There is a need for large prospective studies to provide information on the best management of this disease, especially in high risk groups such as those with cancer.

Introduction

Upper extremity deep vein thrombosis (UEDVT) may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular, or brachiocephalic veins [1] and accounts for 4 to 10% of all cases of deep vein thrombosis. The incidence of UEDVT is increasing, mostly due to the widespread use of central venous catheters (CVC) for parenteral administration of nutrition or drugs [2,3]. Primary UEDVT represents one third of the cases and includes unprovoked UEDVT, effort-related thrombosis (also known as the Paget-Schroetter syndrome), and thrombosis due to the thoracic outlet syndrome. Secondary UEDVT is associated with one or more identifiable triggering factors such as CVCs, pacemakers, or cancer. More than 40% of all patients with UEDVT have concomitant cancer and about 70% of secondary UEDVT are diagnosed in association with the use of a CVC [4].

Acute complications of UEDVT include pulmonary embolism (PE), loss of venous access, arm dysfunction, and CVC-related vein occlusion with or without concomitant infection [4–6]. On the long term, patients with UEDVT are at risk of recurrent venous thromboembolism (VTE), fatal PE, post-thrombotic syndrome of the arm and bleeding during anticoagulant therapy. Information about the clinical outcome of UEDVT is derived from few studies with methodological shortcomings. In addition, the efficacy and safety of anticoagulant therapy for UEDVT remains unclear given the lack of randomized controlled studies. As a consequence, recommendations for UEDVT treatment by the major clinical practice guidelines are largely extrapolated from studies on the management of lower extremity DVT and PE [7]. Current international guidelines recommend LMWH over VKA in cancer patients with VTE, based on a superior efficacy and similar safety profile [8–11].

The aim of the present systematic review was to evaluate the clinical evidence regarding the long-term clinical outcomes of

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UEDVT. The results were stratified by cancer status and by the presence of a CVC, given the potential differences in prognosis and treatment of UEDVT in these cases.

Materials and methods

A systematic search of the literature was conducted in MEDLINE, EMBASE and BIOSIS Previews databases from inception to 2 June 2015 to identify all published articles that evaluated the clinical course of UEDVT. BIOSIS was searched for unpublished information from meetings and reports. Full details of the search strategy are provided in the Appendix. Abstracts and full-text articles were screened independently by two authors (S.M.B. and L.G.) to select articles that met the inclusion criteria. In addition, reference lists of the selected articles were manually screened for potentially eligible studies. Studies were included if they met the following a priori defined criteria: 1) the study was designed as a randomized controlled trial, prospective, or retrospective cohort study, 2) the study included at least 10 adult patients with a first episode of UEDVT, and 3) data were provided on recurrent VTE, mortality or anticoagulant-related bleeding.

The following data were independently extracted by two reviewers (S.M.B. and L.G.) using pre-designed forms: number of patients, study characteristics, follow-up duration, UEDVT etiology, cancer status, presence of a CVC, type of treatment, recurrent VTE, mortality and bleeding complications during anticoagulant therapy. The outcome definitions of the original authors were accepted. All clinical outcomes were extracted for the overall study population and for the subgroups of patients with cancer- and CVC-associated UEDVT. Any disagreements were resolved by consensus or by involving a third reviewer (M.D.N.). An attempt was made to contact the authors in case of missing relevant information.

We assessed the type of study design (prospective, retrospective or unclear), patient enrollment (consecutive, nonconsecutive or unclear), and adjudication of outcome events (yes, no or unclear) as potential sources of bias. A meta-analysis was not performed due to the heterogeneity of the study population and design, and therefore a narrative synthesis of study data is presented. For all outcome variables we described the range and calculated the mean incidence. All statistical analyses were performed in SPSS (IBM SPSS Statistics for Windows, Version 22.0).

Results

Study characteristics

The search yielded 4521 publications, of which 45 studies comprising 4580 patients met the review inclusion criteria (Figure 1). The main characteristics of the included studies are summarized in Table 1. The number of participants ranged from 12 to 598. No randomized controlled trials were identified. The study design was prospective in 11 studies, retrospective in 29, and unclear in 5. Thirty-two studies (71%) enrolled consecutive patients. Outcomes were centrally adjudicated in one study. The follow-up duration was 3 months or less in 5 studies, between 3 and 12 months in 8 studies, more than 12 months in 22 studies, and not specified in the others. Overall, UEDVT was associated with cancer in 44% (range 0 to 74%) and with CVC in 53% (range 0 to 93%) of the cases.

Treatment strategies

Out of 45 included studies, anticoagulant therapy was the mainstay of treatment in 27 (60%; 3271 patients). Initial treatment (i.e. in the first 5 to 10 days) consisted of unfractionated heparin in 13% and low-molecular weight heparin (LMWH) in the remaining 86% of the cases (15 studies, 1781 patients). Among the 24 studies

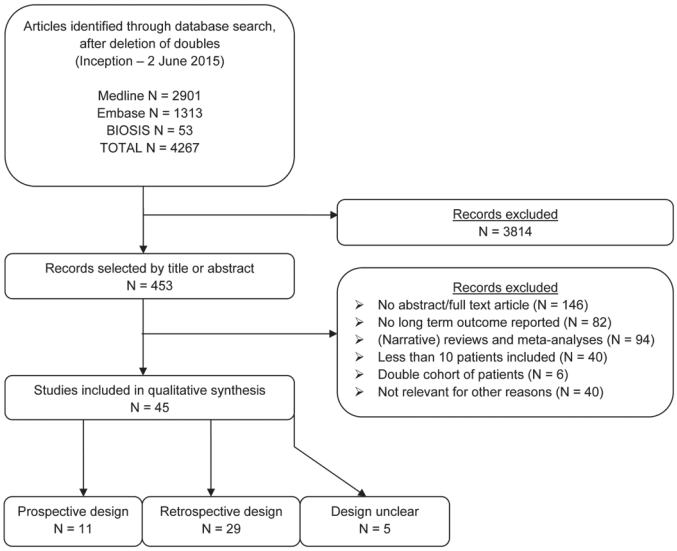

Fig. 1. Flow chart of study selection.

(2636 patients) which reported on long-term treatment, LMWH was used in 32% and vitamin K antagonists (VKAs) in 56% of the patients, for a median duration of 3 to 6 months. In 7 studies, thrombolytic therapy was administered to all patients. In the remaining 11 studies, the treatment strategy was either not reported (2 studies) or heterogeneous (9 studies), including various invasive and non-invasive approaches (Online Table).

In some of the older studies in this review, VKA were prescribed to all cancer patients (12,13). In the study by Muñoz et al from 2008, 75% of the cancer patients received LMWH and 25% VKA. In three studies after 2006 that included cancer patients with CVC-related UEDVT, LMWH was prescribed in the majority of cases [14–16]. In other studies cancer-specific treatment could not be retrieved.

Recurrent VTE

Eleven prospective studies (1661 patients) reported an average incidence of recurrent VTE of 5.1% (range 0 to 13%; Table 2) during a follow-up period ranging from 3 to 59 months. The average incidence of recurrent VTE at 6 months was 3.1% (range 0 to 4.1% in 4 studies) [12,17–19] and 6.5% (range 0–13%) in studies with longer observation periods [16,20–24] (Table 3).

Twenty retrospective studies (1281 patients) reported recurrent VTE in 9.8% (range 0–26%) of patients during follow-up varying from 3 to 62 months [2,13,14,25–41] (Table 3).

Recurrent VTE was defined as symptomatic, objectively confirmed VTE in 12 studies, and as recurrent VTE detected by routine compression ultrasound in 2 studies. A definition was not provided in the other studies. Eighteen studies described the site of recurrent VTE [12–14,18,19,21,23–26,28–30,32–34,39,40]. In 74 (54%) of 138 events, recurrence involved the deep veins of the upper extremities, ipsilateral in 56 (76%), contralateral in 8 (11%), while in 10 cases (14%) the arm was not specified. Twenty-nine recurrent VTE (21%) were PE (including 4 cases of fatal PE) and 10 (7%) were lower extremity DVT. In 25 cases (18%) the exact location of recurrence could not be retrieved.

Two prospective studies evaluated the risk of recurrent VTE in patients with CVC-related UEDVT specifically [18,24] (Table 3). Bauman Kreuziger et al followed 558 patients, including 358 (64%) with cancer, for one year [24]. All patients were treated with anticoagulants. No information about catheter removal was available. The incidence rates of recurrent VTE during anticoagulant therapy were 7 per 100 patient-years, and 3.4 per 100 patient-years after cessation of treatment. Similarly, in a study by Muñoz et al, the