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Original Article

Screening for occult cancer in idiopathic venous thromboembolism — Systemic review and meta-analysis

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ABSTRACT

Background: Idiopathic venous thromboembolism (VTE) may be associated with an occult malignancy. Early detection of cancer might be translated to a better prognosis for these patients. However, the efficacy of extensive screening for cancer in patients with idiopathic VTE is controversial.
Materials and methods: Systemic review and meta-analysis of all available prospective trials comparing extensive to limited screening for occult malignancies in patients with idiopathic VTE.
Primary outcome: all-cause mortality. *Secondary outcomes*: cancer related mortality, early cancer diagnosis, cancer diagnosis at the end of follow up and cancer diagnosis at an early stage. Risk ratios (RR) with 95% confidence intervals (CIs) were estimated and pooled.
Results: The study included five trials and 2287 patients. Extensive screening did not affect all-cause mortality at the end of follow up [RR 0.86 (95% CI 0.58–1.27)] or cancer-related mortality [RR 0.93 (95% CI 0.54–1.58)]. Yet, it yielded more diagnoses of cancer [RR 2.17 (95% CI 1.42–3.32)]. Rates of cancer diagnosis at an early stage did not differ statistically between the two groups [RR 1.49 (95% CI 0.86–2.56)]. However, analysis of the randomized controlled trials alone showed a tendency towards early stage cancer at diagnosis in extensive screening group in, with results almost statistically significant [RR 2.14 (95% CI 0.98–4.67), p = 0.06].
Conclusions: Extensive screening for malignancy after idiopathic VTE does not affect mortality rates. Yet, it yields more cancer diagnoses shortly after the VTE event. Further research is needed to determine whether extensive screening might be proper for specific high risk populations.

1. Introduction

Venous thromboembolism (VTE) is a common disease, accounting for high rates of morbidity and mortality [1]. In approximately 20% of the patients an underlying cause cannot be identified [2], and a diagnosis of idiopathic/unprovoked VTE is made. Detection of an underlying cause of VTE has many clinical implications, one of them is the choice of proper anticoagulation. Unlike other VTE patients, cancer patients will benefit more from low molecular weight heparin in comparison to vitamin K antagonists (as warfarin ([3].

Malignancy related hypercoagulable state is a common etiology for VTE, and is estimated to account for 20–30% of all first VTE events [4]. In 80% of the patients with malignancy related VTE, the diagnosis of malignancy precedes the diagnosis of VTE [5].

The risk of malignancy for patients with idiopathic VTE is significantly higher than for the general population. Iodice et al. showed in a large meta-analysis that the relative risk (RR) for malignancy was 2.7 times higher in patients with idiopathic VTE compared to those without VTE, and 3.8 higher compared to secondary VTE. Both Hematopoietic and solid malignancies were frequently diagnosed following a diagnosis of idiopathic VTE in this large study [6]. A previous meta-analysis found that most occult cancers (10%) were diagnosed in the first year after the diagnosis of idiopathic VTE [7]. It appears that the risk of malignancy is highest during the first year after VTE diagnosis, then it gradually declines and remains only slightly increased compared to general population.

In view of these data, there is a clinical need to define the appropriate evaluation of malignancy following a diagnosis of idiopathic VTE. Such an evaluation may be limited or extensive. As there is no official definition on what limited and extensive screening should include,

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wide variation exits in clinical practice on this subject [8]. Limited testing, as performed in most studies addressing this issue, includes medical history, physical examination, basic laboratory tests, chest X-ray and routine age appropriate cancer screening (such as mammography, and Papanicolaou test (PAP smear)). In a case of abnormal findings suggesting malignancy, further investigation is proceeded [9,10,11]. Extensive evaluation includes the components of the limited approach and additional modalities such as abdominal and pelvic ultrasound (US), total body computed tomography (CT) or positron emission computed tomography (PET – CT FDG), and gastrointestinal endoscopy [9,10,11].

Several studies addressed the issue of screening strategy for patients with idiopathic VTE. Neither one of them demonstrated that extensive screening prolonged survival [9,10,11].

According to the National Institute for Health and Care Excellence (NICE) guidelines published in 2012, patients with idiopathic VTE should go through limited screening. Abdominal CT and mammography (for women) should be considered for patients older than 40, even when no signs of malignancy are apparent on medical history and physical examination [12]. No specific recommendations are provided by other health organizations.

A meta-analysis evaluating the role of extensive screening in patients with idiopathic VTE was published in 2015. It included two trials with a total of 386 patients and demonstrated no survival benefit in the extensive screening group [13]. As other large trials were later published [10,11], we decided to perform a systemic review and a meta-analysis of the current literature, in order to evaluate the role of extensive screening in patients with newly diagnosed idiopathic VTE.

2. Material and methods

2.1. Data sources

The study protocol was written by A.G. and A.K. We conducted a comprehensive search to identify trials in Pub Med (January 1966 to August 2016), the Cochrane Central Register of Controlled Trials (CENTRAL), the conference proceedings of the International Society for Thrombosis and Haemostasis (ISTH) (from 2003 to 2016) and the American Society for Hematology (ASH) (from 2004 to 2016). We used the following search terms: (malignancy or cancer or malignant disease or tumor) AND (screening or detection or diagnosis or evaluation) AND (unprovoked or idiopathic) AND (venous thromboembolism or thromboembolism or VTE or DVT or thrombosis). Conference proceedings were searched using the terms: occult, malignancy, cancer, venous thromboembolism, deep vein thrombosis, pulmonary embolism, screening, evaluating, idiopathic, unprovoked. References of all included trials and reviews identified were scanned for additional studies.

2.2. Study selection

We included all trials which compared limited *vs.* extensive screening for occult malignancies in patients with unprovoked VTE. Types of trials included were randomized controlled trials (RCTs) and prospective non-randomized trials. Trials were included regardless of publication status, date of publication or language.

Two researchers (A.G., A.K.) independently inspected articles identified through the search, based on search terms and inclusion criteria. Any disagreements were resolved by discussion.

2.3. Data extraction and quality assessment

Two reviewers (A.G., A.K.) independently extracted the data from the included studies and assessed independently risk of bias in the included trials. For the RCTs we used the Cochrane Collaboration's tool [16] to assess the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data and selective outcome reporting. We separately assessed each domain and graded it as low, unclear or high risk of bias according to Higgins 2011 [14]. For the non-randomized study, we conducted a separate analysis – the Newcastle Ottawa quality assessment (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Any disagreements were resolved by discussion.

2.4. Definition of outcomes

The primary outcome was all cause mortality at the end of follow up. Secondary outcomes were cancer related mortality at the end of the follow up, the percentage of patients diagnosed with malignancies at the end of the initial screening and at the end of follow up, and early *vs.* advanced stage of malignancy at diagnosis as defined in each study. We aimed to assess rates of recurrent VTE, pulmonary embolism and screening related complication.

2.5. Data synthesis and analysis

We based our analysis according to the intention-to-treat data from the included trials. Dichotomous data were analyzed by calculating the risk ratio (RR) for each trial with 95% confidence interval (CI) (Review Manager [RevMan], version 5.1 for windows, The Cochrane Collaboration, Oxford, United Kingdom). We assessed heterogeneity of trial's results by calculating a chi-square test of heterogeneity and the I^2 measure of inconsistency. We used a fixed effect model with Mantel-Haenszel method for pooling trial results throughout the review unless statistically significant heterogeneity was found ($p < 0.10$ or $I^2 > 50\%$), in which case we chose a random- effects model and use the DerSimonian and Laird method [15].

We aimed to explore potential sources of heterogeneity through sub-group analyses of the primary outcome according to different baseline parameters: age > 60, previous cancer, smoking status, time of randomization after VTE diagnosis (within 6 months compared with after 6 months), co-morbidities and medication usage, such as oral contraceptives and hormonal replacement therapy (HRT). In addition, we conducted sensitivity analyses according to the design of the trials – assessing RCTs separately.

3. Results

The search of electronic databases yielded 461 studies. In addition, one trial was identified by searching conference proceedings- ISTH 2012. Twenty-four were considered potentially relevant. Of the 24 studies, 19 were excluded for various reasons, mainly because these articles were non-comparative and did not include two arms of limited and extensive screening. The process of study selection according to PRISMA is illustrated in Fig. 1. Five trials conducted between 2004 and 2016 met the inclusion criteria. Four of these trials were RCTs [9,10,11,16], and one trial [17] was a prospective open label trial without randomization. Of the RCTs, 1 trial was published as an abstract [16].

3.1. Study characteristics

A total of 2287 patients were included in five trials [9,10,11,16,17]. Most patients (1657, 72.4%) were included in four RCTs [9,10,11,16], of which, 1644 (>99%) patients were evaluable for outcome and safety assessment. Studies and patients' characteristics and the description of the components of extensive testing are summarized in Table 1. The mean age of the patients ranged from 53.7 to 71 in the included trials. Forty percent of participants were women. Smoking status was reported in four out of five trials [9,10,11,17]. The average percentage of smokers was 36.5% in all studies included. The median follow up periods ranged from one year to 2.5 years. The limited screening protocol was similar between the trials and included medical history, physical examination, blood tests and chest X-ray. Two trials [10,11] included age appropriate screening tests such as mammography, PAP smear and

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