CT-venography compared to duplex ultrasound for detection of catheter-related thrombosis in cancer patients

Published: 29-11-2021
Last updated: 30-11-2024

The main objectives of this study are(I) to compare the sensitivity of CT-venography and ultrasound for screening-detected, catheter-related thrombosis in cancer patients and (II) to assess intrinsic coagulation levels in cancer patients prior to...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON49895

Source
ToetsingOnline

Brief title
DETECT study

Condition

- Miscellaneous and site unspecified neoplasms benign
- Embolism and thrombosis

Synonym
Cancer/malignancy; venous thomboembolism/blood cloth

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Central Venous Catheters, Diagnostic imaging, Neoplasms, Venous Thromboembolism

Outcome measures

Primary outcome

The primary outcome is the composite of:

1. Screening-detected, clinically relevant, ipsilateral upper extremity deep-vein thrombosis at the discretion of the local radiologist, demonstrated by one of the following:

- A non-compressible venous segment or abnormal flow on ultrasound;

- An adjudicated vascular filling defect, detectable in at least 50% of the lumen around the catheter on CT-venography;

- An adjudicated vascular filling defect in the non-cannulated deep veins on CT-venography.

Upper extremity deep veins include the brachial, axillary, subclavian, brachiocephalic, jugular, and superior caval vein.

2. Screening-detected, clinically relevant pulmonary embolism at the discretion of the local radiologist, demonstrated by an intraluminal filling defect in a segmental or more proximal pulmonary artery on CT-venography.

Secondary outcome

Secondary endpoints include

- Intrinsic pathway activation at baseline and during follow-up, assessed by levels of FXIIa:C1inh, FXIIa:AT, FXIa:C1inh, FXIa:AT, FXIa:a1AT, pKa:C1inh, and FIXa:AT complexes, and a factor XIa-dependent thrombin generation test.

- Clinically relevant venous thromboembolism

- Non-clinically relevant thrombi

- Catheter malfunction

- Major bleeding

- Clinically relevant non-major bleeding

- All-cause mortality

- Allergic reaction to contrast agents

- Reported contrast nephropathy

- Initiation of anticoagulant therapy in patients with screening-detected

upper-extremity deep-vein thrombosis and/or pulmonary embolism.

Study description

Background summary

Catheter-related thrombosis, defined as mural or occlusive upper-extremity deep-vein thrombosis (DVT) within the cannulated vein or a contiguous vein, is a common and burdensome complication in patients with central venous catheters, in particular in those with cancer. Sequelae of catheter-related thrombosis are loss of vascular access, post-thrombotic syndrome of the upper extremity, vena cava superior syndrome, or pulmonary embolism. PICCs have been reported to double the risk of thrombosis compared to other CVCs.

Patients with catheter-related thrombosis may present with symptoms (e.g. ipsilateral upper-extremity edema, redness, pain), but they may also remain asymptomatic. Therefore, screening for catheter-related thrombosis is frequently used to assess the efficacy of anticoagulants in clinical studies, under the assumption that the number of asymptomatic screening-detected events is a reflection of the number of symptomatic events. Currently, the diagnostic modality of choice for catheter-related thrombosis screening is duplex ultrasound of the upper extremity, ideally combined with compression. Advantages of ultrasound as compared to other diagnostic modalities include its widespread clinical utility, portability, non-invasive nature without exposure to ionizing radiation, and that it provides information on the flow direction. However, it is a rather operator dependent modality, and also central veins are

less accessible using ultrasound, leading to lower accuracy. In a recent meta-analysis, the sensitivity for ultrasound in detection of symptomatic upper extremity DVT was reported to be 85%, indicating that 15% of the clots are missed. Data on the sensitivity of ultrasound for screening-detected events are scarce. Upper extremity CT-venography is another diagnostic modality that may be used for catheter-related thrombosis-screening. Although CT-venography is a procedure involving ionizing radiation, recent advances in CT technology enable imaging with a low effective dose equivalent to background radiation. Accumulating evidence on CT-venography for detection of lower extremity thrombosis suggests that CT-venography is as accurate as ultrasound for detection of thrombosis and may additionally reveal thrombi in more central veins such as the brachiocephalic and superior caval vein. In addition, the small amount of contrast in the pulmonary arteries may allow for occasional detection central emboli. Furthermore, CT-venography images allow for central adjudication, with the ability to achieve more consistent, independent, and unbiased results in clinical trials. Despite these potential benefits, data on the accuracy of CT-venography for catheter-related thrombosis or upper-extremity thrombosis in general are lacking, which hampers its use for screening in clinical studies.

Although current international guidelines suggest thromboprophylaxis with low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOAC) in cancer patients at high risk of thrombosis, routine prophylaxis for prevention of catheter-associated thrombosis is not recommended, because of uncertainty about the benefits and harms in cancer patients with CVCs. One of the main pathophysiological mechanisms leading to catheter-related thrombosis is induction of the intrinsic coagulation pathway. As the intravascular catheter forms an artificial surface and lacks an endothelial layer, it directly activates coagulation factor (F)XII, the initiator of the intrinsic coagulation pathway. FXIIa will subsequently activate a series of serine proteases (FXI, FIX, FX as well as prekallikrein [pKa]), which ultimately leads to thrombin generation. In recent years, several drugs have been developed that target the intrinsic coagulation pathway. An open-label phase II study in patients undergoing knee arthroplasty demonstrated that FXI antisense oligonucleotide (hepatic FXI synthesis inhibitor) 300 mg dosed once was more effective than standard-of-care enoxaparin (LMWH) once daily (VTE risk 4% vs. 30%) with less bleeding (3% vs. 8%). Given the important role of the intrinsic coagulation pathway in the development of catheter-related thrombosis in cancer patients, intrinsic pathway inhibitors may also be effective in this population. However, additional data is needed on the level of intrinsic activation markers in cancer patients to determine dosage and time of administration before catheter placement.

The main aim of this study is to determine whether CT-venography offers an accurate alternative to duplex ultrasound for detection of PICC-related upper-extremity DVT and PE in asymptomatic cancer patients. Secondary aims include to assess intrinsic coagulation marker levels in cancer patients prior

to and after PICC-placement in patients with and without thrombosis during follow-up.

Study objective

The main objectives of this study are
(I) to compare the sensitivity of CT-venography and ultrasound for screening-detected, catheter-related thrombosis in cancer patients and
(II) to assess intrinsic coagulation levels in cancer patients prior to and after PICC-placement.

Other objectives include to evaluate of the proportion of patients initiating anticoagulant therapy for treatment of screening-detected thrombi on ultrasound and for treatment of screening-detected thrombi on CT-venography, the risk of any symptomatic or asymptomatic VTE, the risk of catheter malfunction, the risk of major or clinically relevant non-major bleeding according to ISTH definitions, all-cause mortality in cancer patients at 25 days after PICC-placement.

Study design

This is a prospective cohort study that will be performed at the Amsterdam University Medical Center (UMC), locations AMC and VUmc (clinical part), and the Maastricht University (laboratory part).

Intervention

Ultrasound and CT-venography for catheter-related thrombosis screening.

Study burden and risks

At baseline, patients will be assessed for signs of thrombosis and blood will be drawn for laboratory analysis, followed by PICC placement. At day 7±3, a second blood withdrawal will be performed (in a subset of) patients on a voluntary basis. During a follow-up visit at day 20±5, patients will be assessed for signs of thrombosis or bleeding, blood will be drawn, and a screening ultrasound and CT-venography will be performed. The burden of the study includes one additional hospital visit, two or three blood withdrawals, an ultrasonography, and CT-venography, which exposes patients to ionizing radiation and the risk of contrast-induced nephropathy or allergic reactions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age 18 to 80 years
- Diagnosis of solid or haematological cancer
- Planned PICC placement for administration of systemic cancer therapy or other indications
- Ability to provide written informed consent

Exclusion criteria

- Extremity DVT within 6 months prior to catheter insertion
- Inserted central venous catheter within 12 hours prior to inclusion
- Mechanical heart valve or pacemaker
- Ongoing therapeutic anticoagulation
- Known pregnancy
- Creatinine clearance <30 mL/min (estimated using CKD-EPI equations)
- Solitary kidney (either functionally or anatomically)

- Allergy to contrast agents
- Anticipated referral to another hospital within a few days after PICC placement

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-04-2022
Enrollment:	285
Type:	Actual

Ethics review

Approved WMO

Date:	29-11-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL78101.018.21