A randomised controlled multicenter trial comparing ultrasound-accelerated catheter-directed thrombolysis combined with standard anticoagulant therapy versus standard anticoagulant therapy alone for acute primary iliofemoral deep vein thrombosis (IFDVT).

Published: 21-12-2009
Last updated: 06-05-2024

Primary Objective: Can catheter directed thrombolytic therapy, for the treatment of primary IFDVT, safely and effectively reduce post thrombotic morbidity after one year?Secondary Objective: Does catheter directed thrombolytic intervention have a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON45108

Source
ToetsingOnline

Brief title
CDT or conventional anticoagulant therapy in DVT.

Condition

- Vascular therapeutic procedures
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym

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thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: academisch ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Catheter-directed, Deep Vein Thrombosis, Ilio-femoral, Thrombolysis

Outcome measures

Primary outcome

Percentage of patients with PTS charactarized by a Villalta-Prandoni score * 5 on two consecutive occasions of at least 3 months apart, or presence of a venous ulcer one year following the acute thrombotic event. (Villalta-Prandoni: score 5-9 = mild PTS, score 10-14 = moderate PTS, score * 15 or venous ulcer = severe PTS)

Secondary outcome

* The Health Related Quality of Life (HRQOL) based on scorings on SF-36, EuroQOL-5D, pain disability index and VEINES-QOL/Sym (t3,6,12 months after the event)

* Late PTS during follow-up

* Recurrent venous thrombo-embolisms (VTE): DVT (measured by CUS) or pulmonary embolism (PE) (objectivated by spiral CT-angiography) during follow-up

* Clot lysis, patency (measured by duplex ultrasound and MRA-gadofosveset trisodium(Vasovist or ablavar) at t0 and 12 months, which shows the percentage of occlusion of all visualized veins) and valve function (measured by APG

imaging at t0 and 12 months)

* Measurements of markers of coagulation and inflammation (at t0 and 12 months)

Study description

Background summary

Iliofemoral deep venous thrombosis (IFDVT) is associated with significant post thrombotic morbidity. Approximately 95% of patients with IFDVT treated with anticoagulant medication have valve incompetence after 5 years. Even more serious is the relatively high incidence, between 50% and 90%, of Post Thrombotic Syndrome (PTS) among those patients. PTS is characterized by a painful, heavy leg, with cramps, paresthesia, pruritus, formation of varicosities, edema and/or hyperpigmentation of the skin with reduced QOL. In severe cases (3-5%) PTS even leads to non-healing, extremely painful venous legs ulcers. Early thrombolysis may reduce the incidence of PTS as compared to treatment with conventional anticoagulant medication alone. Normal valve function is more likely retained after early clot lysis. It is suggested that the presence of both obstruction and reflux, rather than either of these alone, significantly increases the chances for development of PTS.
Although promising, until now most evidence on catheter directed thrombolysis (CDT) is derived from case series and little evidence is derived from randomized clinical trials. Moreover in most cases non informative outcome measures, like valvular competence, are used instead of incidences of PTS. Systemic thrombolysis reduces the one year incidence of PTS as compared to treatment with anticoagulant therapy alone (67% versus 89%), but is associated with bleeding complications due to a relative high dosage of Urokinase (UK) (8% versus 0%). Bleeding complications are reduced (0-3,8%) and recanalisation increased using CDT with UK versus systemic thrombolysis with UK (complete lysis resp. 76-90% versus 28%). Ultrasound accelerated CDT (UACDT) further reduces complications, treatment time/dose and improves results.
Catheter directed thrombolysis therapy has the potential to be a good candidate for frontline therapy for IFDVT. However, due to the relative absence of high quality evidence derived from prospective randomized controlled clinical trials it seems imperative to conduct a prospective randomized study to compare the safety and efficacy of catheter directed thrombolysis to conventional anticoagulant therapy for IFDVT in relation to the development of post thrombotic morbidity.
Additional therapeutic advantages of surgical interventions such as improvement of the health related quality of life (HRQOL) have been reported. We hypothesize that such improvements could also be reached after catheter directed thrombolysis, we therefore will also include HRQOL questionnaires in

our prospective study.

Study objective

Primary Objective: Can catheter directed thrombolytic therapy, for the treatment of primary IFDVT, safely and effectively reduce post thrombotic morbidity after one year?
Secondary Objective: Does catheter directed thrombolytic intervention have a positive effect on the quality of life of patients with primary IFDVT?

Study design

We propose to conduct a prospective randomized controlled study comparing catheter directed thrombolysis with conventional anticoagulant therapy to conventional anticoagulant therapy alone for patients with acute IFDVT.
Consecutive patients admitted to the emergency room or outpatient department of the participating centres will be recruited after confirmation of IFDVT.
Patients recently diagnosed with IFDVT at non-participating centres (or their treating physicians) are allowed to contact our investigators and to participate (when inclusion and exclusion criteria are met). Patients will be contacted, informed and offered the opportunity to participate in the study.
After randomization patients will be allocated to either conservative treatment alone or to catheter directed thrombolysis combined with conservative treatment.
Conservative treatment consists of compression therapy for 24 months and anticoagulant treatment with an initial treatment with therapeutic doses of LMWH (fraxiparine/fraxodi®,) in combination with vitamin K-antagonists (acenocoumarol® and fenprocoumon®, Addenum B2 * Dosing schemes), followed by treatment with vitamin K-antagonist alone (after completing LMWH treatment of at least 5-7 days and after an INR above 2 has been reached on two consecutive measurements) Or NOACs. Anticoagulant treatment will be installed according to national and international guidelines (ACCP 2008, CBO 2008) tailored based on the character of the event (6 months of therapy for idiopathic DVT and 3 months for provoked DVT).
Catheter directed thrombolysis will be performed in a sub-acute stage of IFDVT, but no later than 21 days after the onset of complaints. Patients will be admitted to a clinical ward of one of the participating centerst for the duration of the active lysis, this will be between 24-96 hours (1-4 nights).
The catheter directed thrombolysis will be performed by a experienced intervention-radiologist with an Ekos Endowave® system (EKOS Corporation, Bothell, WA; Addendum C1 * Product information Ekos Endowave®, including C2 * *CE-markering*). Catheter-directed thrombolysis is a routinely used system for thrombosis in intervention-radiology. The Ekos Endowave® system uses a standard guide wire to position the Intelligent Drug Delivery Catheter across the length of the target clot. The guide wire is then pulled out and replaced with the Microsonic core (with several miniscule high frequency (2MHz) ultrasound

transducers). The system automatically monitors and controls the microsonic energy delivery. This system does not fragment the thrombus but only gives a structural change by which a better penetration of the thrombolytic agent is achieved. This method is especially suitable for use around venous valves. Ultrasound techniques are able to penetrate the thrombus around the valve without destroying the valve itself.
The advantages of the Ekos Endowave-system are that only a small amount of thrombolytic agent is needed and that the infusion time is significantly reduced compared to other catheter-directed thrombolytic techniques, thereby reducing the chance for bleeding complications.
Visits to the outpatient clinic will take place at 3 months, 6 and 12 months after the event, 3 visits in total. At each visit signs and symptoms of PTS will be recorded (Villalta-Prandoni, Venous Clinical Severity Score, (VCSS)).
Patients will be followed for the entire duration of the study; assessments on symptoms of PTS (including Villalta-Prandoni score, VCSS and duplex ultrasound assessment) and HRQOL will be offered once every year. During the final year of the study (the year following inclusion of the last study patient), the visits as part of the extension fase will be clustered on set dates .
Within one week of inclusion and before the visit at 12 months patency of the venous system will be examined for all patients by MRA-gadovist and duplex and/or APG . Patency scores as well as PTS scores will be compared between patients from the intervention group and patients from the conventional therapy group.
Costs associated with transport to and from the participating centres for additional imaging (all patients at t0,12 months) and/or thrombolysis (intervention-group only) will be restituted according to standard guidelines (0,19 ¤ / km).

Intervention

Catheter directed thrombolysis will be performed with an Ekos Endowave® system (EKOS Corporation, Bothell, WA). The system uses a standard guide wire to position the Intelligent Drug Delivery Catheter across the length of the target clot. The guide wire is introduced through the popliteal vein. Along the guide wire the catheter is positioned. The location of the dispersion catheter is controlled and if necessary adjusted by X-ray. The guide wire is then pulled out and replaced with the Microsonic core (a miniscule high frequency (2MHz) ultrasound transducer). The system automatically monitors and controls the microsonic energy delivery. This system does not fragment the thrombus but only gives a structural change by which a better penetration of the thrombolytic agent is achieved. This method is especially suitable for use around venous valves. Ultrasound techniques are able to penetrate the thrombus around the valve without destroying the valve itself. The advantage of the Ekos Endowave-system is that only a small amount of thrombolytic agent is needed, thereby reducing the chance for bleeding complications. The nature and the duration of the installed anticoagulant therapy following the intervention will match the therapy installed in the comparator group. It is expected that in

approximately 60% of patients there will remain a significant venous obstruction after Ekos endowave® thrombolysis. This will be treated by percutaneous transluminal angioplasty with stenting.

Study burden and risks

The most serious side effect of thrombolytic therapy is bleeding. With catheter directed thrombolysis the total thrombolytic dose is significantly less than the dose administered with the systemic approach. Localized thrombolysis thereby minimizes complications due to bleeding. One retrospective study (Parikh et al, 2008) with the Ekos endowave® system reports major bleeding rates of 3.8% (2/53), involving NO retroperitoneal or intracranial bleedings. Furthermore the 2 reported bleedings both occured in postoperative patients.

We therefore think that the current study is justified, more so considering the fact that a safety analysis will be performed at 6 months after study start to assess the eventual excess morbidity/mortality rate due to bleeding.

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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 between 18-85 yrs, objectively documented IFDVT at least no patency in the common femoral vein, acute stage (6 months, first thrombus in the affected leg,

Exclusion criteria

History of GI bleeding within 12 months, History of CVA/CNS disease whitin 12 months, Severe hypertension (>180/100 mmHg), Active malignancy, Major surgery within 6 weeks, Previous thrombosis of the affected limb, Varicositas/venous insufficiency, (CEAP classification C3 or higher) Pregnancy, ALAT > 3 times normal range, GFR < 30 mL/min , permanent wheelchair dependency

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2010
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	21-12-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-03-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-06-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-06-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-07-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-07-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-08-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	14-11-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-03-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-04-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-12-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-05-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-01-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT00970619
CCMO	NL28394.068.09

Study results

Date completed:	01-12-2018
Actual enrolment:	184