Current use of anticoagulants in cirrhosis: a prospective study.

Published: 12-12-2016
Last updated: 16-04-2024

Primary Objective: To assess whether the current use and dosing in cirrhosis of anticoagulation is as effective in inhibiting ex vivo thrombin generation compared to the treatment of patients with competent liver function

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational invasive

Summary

ID

NL-OMON43138

Source
ToetsingOnline

Brief title
CURRENT study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Hepatic and hepatobiliary disorders

Synonym
end-stage liver disease, liverfibrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anticoagulants, cirrhosis

Outcome measures

Primary outcome

This study will measure the percentual difference of ex vivo thrombin generation capacity of plasma before and after anticoagulation compared to patients without cirrhosis. The primary endpoint is the difference between anticoagulant potency (as expressed by percentual decrease in thrombin generation) of prophylactic or therapeutic anticoagulation in patients versus controls.

Secondary outcome

Other study parameters that will be observed are the incidence of bleeding and thrombosis untill 3 months after the event or admission. This information will be gathered from the patients* medical chart. If present data on the resolution of thrombosis during or after anticoagulant treatment will be collected (max 3 months). Also information on previous thrombotic events and previous use of anticoagulants will be collected. Prothrombin time, activated partial thromboplastin time, factor II, I and Xa-activity will be measured from the same samples of which the thrombin generation capacity is tested.

Study description

Background summary

Cirrhosis represents irreversible destruction of the liver parenchyma which occurs in response to multiple conditions and diseases. Due to persistent cell

damage, liver function is impaired (1). One of the central roles of the liver is to provide a balanced hemostastic system by manufacturing coagulation proteins and factors. Consequently chronic liver failure, i.e. cirrhosis, results into profound changes in this hemostatic system, which leads to a new but delicate balance. As a resultant of this delicate balance there is an increased susceptibility to bleeding as well as thrombotic events (2, 3), with a twofold increase in relative risk for venous thromboembolisms in cirrhosis compared to matched controls (4). Portal vein thrombosis, in particular, has a reported incidence of up to 40% in end stage cirrhosis (5).

Historically, patients with cirrhosis were considered to be *auto-anticoagulated* as evidenced by an increased INR and reduced platelet count. Large epidemiological studies have definitevely shown that patients with liver disease are not protected from thrombotic disease, but are rather at increased risk. Nevertheless many physicians are still reluctant to use antithrombotic therapy in these patients, due to a (perceived) bleeding risk, despite accumulating evidence that antithrombotic therapy in patients with cirrhosis has a favorable safety profile. The lack of guidelines focusing on the optimal anticoagulant treatment in cirrhosis precipitates cautious prescribing.

Until recently vitamin K antagonists (VKA) have been the preferred drugs in the treatment of venous thrombo-embolisms in patients without liver disease. Since several years, VKAs have been abandonded as first line treatment for the prevention of cerebrovascular events in non-valvular atrial fibrillation. Currently direct oral anticoagulants (DOAC) are the recommended anticoagulant treatment for these specific indications mainly due to the significantly reduced risk of intracranial hemorrhage (6-13). Unfortunately patients with impaired liver function were excluded from large phase 2 and 3 trials in which safety and efficacy of DOAC were tested compared to traditional anticoagulant therapy.

Correct dosing and monitoring of VKA is regulated by means of INR. Standard treatment is adjusted to a prespecified target range, which is unclear in patients with cirrhosis, due to the already prolonged INR (14). The use of LMWH is relatively safe for patients with cirrhosis in the treatment and prevention of portal vein thrombosis or venous tromboembolism (15-18) However the mode of administration, subcutaneous injections twice a day, is strenuous and might impair long term use and adherence.
Next to the INR, the traditional coagulation tests, prothrombin time (PT) and activated partial thromboplastin time (APTT) are a poor reflection of the true hemostatic profile of patients with cirrhosis. Thrombin generation testing in the presence of thrombomodulin, which assesses the real balance of pro- and anticoagulant factors, provides a reliable measurement on the effects of drugs on the hemostatic profile of patients with cirrhosis (19-21).
There is still little data on the use of all (traditional and DOAC) anticoagulant drugs in patients with cirrhosis. They are presented with different advantages and disadvantages, which complicates the treatment of

thrombosis even more. In this study, the efficacy of current anticoagulant therapy in cirrhotics is assessed by thrombin generation tests before and after administration of a single dose of the prescribed drug compared to matched healthy controls.

Study objective

Primary Objective: To assess whether the current use and dosing in cirrhosis of anticoagulation is as effective in inhibiting ex vivo thrombin generation compared to the treatment of patients with competent liver function

Study design

This study has a case controlled observational design in which patients with cirrhosis will be subsided to two venous punctures at two time points during recently initiated anticoagulation therapy in the context of routine care. We will include consecutive patients meeting inclusion criteria during a time frame of two years and compare their results to age, gender, therapy and in-outpatient status matched controls. Blood samples will be taken before and after the start of anticoagulant treatment (prophylactic or therapeutic).

Study burden and risks

This study could possibly lead to essential information in order to perform future studies concerning the choice and dosage of anticoagulation in cirrhosis. The intervention of this study contains the collection of two blood samples and is considered negligible.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients:
- Age over 18 yrs
- Diagnosed with cirrhosis according to one of the following criteria:
a Fibroscan suggestive for F4 fibrosis
b Histology compatible with severe fibrosis (Metavir F4)
c Physician*s reports
- Written informed consent
- (Future) indication to start anticoagulant therapy (prophylactic or therapeutic) ;Controls:
- Age over 18 yrs
- Written informed consent
- Indication to start anticoagulant therapy (prophylactic or therapeutic)

Exclusion criteria

Patients:
- Malignancy;Controls:
- Malignancy
- Auto-immune disease
- Documentation of inherited bleeding disorders
- Cirrhosis

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-12-2016
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO

Date:	12-12-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL57834.042.16