Prothrombin complex concentrate in the reduction of blood loss during orthotopic liver transplantation.

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To investigate in a randomized controlled trial, whether giving Cofact pre-operatively can reduce the bloodloss and transfusion requirements during orthotopic liver transplantation. Also we investigate the safety of Cofact in this patient population...

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

Summary

ID

NL-OMON40112

Source
ToetsingOnline

Brief title
PROTON-study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Bleeding, hemorrhage

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Sanquin Bloedbank,Sanquin Plasma Products

Intervention

Keyword: Blood loss, Coagulation, Liver transplantation, Prothrombin complex concentrate

Outcome measures

Primary outcome

1) Number of RBC (red blood cell) units transfused during and immediatly after

liver transplantation.

Secondary outcome

1)The number of units of fresh-frozen plasma

2) Units of platelet concentrate

3) Fibrinogen concentrate administration

4) Calculated Hb loss

5) Antifibrinolytic drugs

6) Crystalloids or colloids administered, the number of units of allogeneic and

autologous (if used)

7) Other escape medication used

8) Amount of blood loss and amount of ascites loss

Study description

Background summary

Patients with end stage liver disease frequently develop clothing disorders as a result of decreased synthetic capacity of the liver. It is assumed that patients with end stage liver disease, due to decreased coagulation factors and disturbed coagulation tests, have an increased bleeding risk. This is reflected in prolonged prothrombin time (PT) and activated partial thromboplastin time(APTT), and in a increased risk for bleedingcomplications during orthotopic liver transplantation (OLT). Preoperative PT and INR however, do not predict bleeding risk and the risk of transfusion during OLT.

In the past years, there has been a decrease in blood loss and transfusion requirements due to improvements in surgical techniques and a restrictive transfusion policy. Nevertheless, there is a substantial risk for bleeding during OLT and severe bleeding complications still occur.
Transfusion products like red blood cells (RBC), platelet concentrates, fresh frozen plasma clotting factors (FFP) and fibrinogen have not led to a further decrease in blood loss during OLT. Transfusion complications are well described in literature, and are mainly caused by volume overload by these high volume transfusion products. In particular, transfusion of multiple units can result in a volume overload in a already hyperdynamic circulation due to portal hypertension, resulting in more bleeding. It has been proven in clinical studies that a restrictive transfusion policy decreases blood loss during OLT. The fact that transfusion products are not contributing in decreasing blood loss has probably more to do with the hemodynamics, the hemostatic effect thus disappears to the background.
Cofact (prothrombin complex concentrate), in contrast to transfusion products mentioned above, is a low-volume mixture of 4 procoagulants, among which prothrombine. We expect that pre-oprative intravenous administration of Cofact will decreases per operative and postoperative blood loss and transfusion requirements. Also we want to investigate the safety of Cofact in regards to thrombotic complications in this patient group.

Study objective

To investigate in a randomized controlled trial, whether giving Cofact pre-operatively can reduce the bloodloss and transfusion requirements during orthotopic liver transplantation. Also we investigate the safety of Cofact in this patient population.

Because of difficulty in assessing the total volume of blood loss during orthotopic liver transplantation (for example because of ascites admixture), we have chosen the transfusion of RBC as primary objective.

Study design

A multicentre double-blinded placebo controlled randomized trial.

Intervention

Intravenous administration of Cofact to the studygroup during induction of anesthesia.

Study burden and risks

Because Cofact consist of procoagulants, there is a theoretical risk for thrombotic complications. Clinical studies, however, dont confirm this risk.

Also, patients will go preoperatieve thromboelastography to exclude hypercoagulability. Patients that show hypercoagulability will be excluded.

The risk for transmittable infectious diseases cannot fully be excluded because Cofact is made out of human plasma. The risk for transmittance is minimalized by testing and screening the donor for past exposure to certain viruses. By testing donors for the presence of certain current viral infection, en by inactivation and elimination of certain viruses, the risk for transmission is further reduced.

The total duration of hospital stay and course is mostly similar to patients undergoing liver transplantation and not participating in this study. The exception lies in a electrocardiogram study at day 3 and 7 post-operatively. This study has minimal discomfort for patient, a few electrodes are placed of patients body and he/she has to lie still for a few minutes. This extra study is being performed in eye of patient safety. The polyclinic follow-up is the same as with other liver transplantation patients.

There is a small risk for allergic or anafylactic reaction to the study product Cofact. In case of such an event, treatment with Cofact will be ceased immediately. A severe anafylactic reaction can lead to shock and can be lifethreatening. There is expertise in every participating centre to manage and treat such an event.

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

- At least 18 years
- Eligible for OLT
- Signed informed consent

Exclusion criteria

- Split liver transplantation
- Heterotopic liver transplantation
- Scheduled multiorgan transplantation
- Scheduled living related-donor transplantation
- Documented congenital coagulation disorders
- Documenten history or presence of arterial or venous thrombosis
- Treatment with coumarin
-Acute hepatic failure without previous known history of hepatic disease
- Coronary artery disease
- Documented history of thrombophilia
- Hypercoagulability assessed by preoperative thromboelastography

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2013
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cofact
Generic name:	Prothrombin Complex Concentrate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-05-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2015
Application type:	Amendment
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
EudraCT	EUCTR2011-005650-54-NL
CCMO	NL38867.042.12