Efficacy and safety of Haemocomplettan® P in patients experiencing microvascular bleeding while undergoing elective complex cardiac surgery

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To determine whether fibrinogen concentrate infusion reduces perioperative blood loss and transfusion in patient experiencing clinically relevant microvascular bleeding during elective complex cardiac surgery and to determine whether its use is safe...

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

Summary

ID

NL-OMON34087

Source
ToetsingOnline

Brief title
Fibrinogen concentrate during elective complex cardiac surgery.

Condition

- Cardiac therapeutic procedures

Synonym
bleeding, microvascular bleeding during complex cardiac surgery

Research involving
Human

Sponsors and support

Primary sponsor: Isala Klinieken
Source(s) of monetary or material Support: eigen onderzoek Maatschap Anesthesiologen Zwolle

Intervention

Keyword: complex cardiac surgery, fibrinogen, Haemocomplettan® P, microvasculair bleeding

Outcome measures

Primary outcome

Perioperative blood loss measured as blood loss in ml between infusion of study

medication and closure of chest.

Secondary outcome

1. Postoperative blood loss, measured as blood loss at the ICU between closure

of chest and:

• 1st hour

• 2nd hour

• 3rd hour

• 6th hours

• 12th hours

• 24th hours

• At the actual time of chest tube removal.

2. Number of units of allogenic blood products (platelets + FFP + RBCs)

administered to subjects, between administration of study medication and

closure of chest.

3. Number of units of allogenic blood products administered to subjects,

between administration of study medication and 24 hours thereafter.

4. Number of units of allogenic blood products (platelets + FFP + RBCs) administered to subjects, from admission to the ICU to discharge to the ward.

5. Number of units PPSB or Novoseven given in the peri- and postoperative period.

6. Duration of post CPB phase, from infusion of study medication to transfer to ICU

7. Ventilation-time in hours during ICU stay.

8. Duration of stay in hours in the ICU following last suture of the initial surgery.

9. Duration of hospital stay in hours following last suture of the initial surgery.

10. Proportion of subjects that receive a follow-on surgery to correct unacceptable bleeding within 5 days of last suture.

11. Wound, sternal or other types of infection.

12. Major clinical events:

o Mortality at 30 days post-surgery

o MACE (major adverse cardiac event)

o Cerebrovascular accident/ transient ischemic attack

o Renal insufficiency or failure

o Venous thromboembolism/ pulmonary embolism

o Allergic or other systemic reaction to study medication

Study description

Background summary

Complex cardiac surgery is often complicated by excessive peri and postoperative bleeding, most frequently due to insufficient surgical haemostasis, impairment of the coagulation system, or both. A common response to excessive bleeding is transfusion of allogeneic blood products. However, this is known to be associated with adverse events, increase in operation time, significant cost, and early and late mortality. The use of blood preservation methods and more judicious transfusion of blood products are therefore necessary. One of the promising new developments in blood preservation techniques is the use of fibrinogen concentrate, which is the key substrate for blood coagulation. Commercially available fibrinogen concentrate is indicated for the reversal of the coagulopathy found in congenital hypo-, dys-, and afibrinogenaemia and in acquired hypofibrinogenaemia. Acquired hypofibrinogenaemia as a result of dilution and/or consumption is the most common cause of low fibrinogen levels, which induces coagulation disorders that may lead to severe bleeding.
Fibrinogen concentrate is increasingly used to treat excessive bleeding due to acquired coagulopathy with low plasma fibrinogen levels. Due to a lack of randomized clinical studies, it is unknown to which extent fibrinogen concentrate reduces blood loss and whether its use is safe. We designed this trial to answer these questions.

Study objective

To determine whether fibrinogen concentrate infusion reduces perioperative blood loss and transfusion in patient experiencing clinically relevant microvascular bleeding during elective complex cardiac surgery and to determine whether its use is safe and well-tolerated.

Study design

This study is a single center, prospective, randomized, double-blind, placebo-controlled, phase II study.

Intervention

Patients with microvascular bleeding after removal of CPB are randomized to receive Haemocomplettan® P (human fibrinogen concentrate, pasteurized) or placebo (human albumin). Dosing will be individually determined based upon plasma fibrinogen levels measured during the reperfusion-rewarming phase during cardiopulmonary bypass.
Formula for Haemocomplettan® P infusion:

(2.5 - [plasma fibrinogen on CPB g/L]) x (1-Ht on CPB) x 0.07 x body weight (kg) = whole g Haemocomplettan® P to be infused. Infusion will be calculated as total g/L, allowing adequate preparing of the commercially available 1g/L vials of Haemocomplettan® P.
For placebo an equivalent volume of placebo will be infused.

Study burden and risks

Burden:

o The patient will undergo doppler-echography of the lower extremity 1 day prior to surgery and 3 days after surgery.

Risks:
The next side-effects can be expected:
o Allergic reaction
o Fever
o Headache
o Nausea and vomiting
Above side-effects are reported in a little more than 1% of patients

- Risk of transmission of infectious agents due to use of human plasma derivative.
- Risk of thromboembolic events.

Contacts

Public
Isala Klinieken

Groot Wezenland 20
8011 JW
NL
Scientific
Isala Klinieken

Groot Wezenland 20
8011 JW
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eighteen years of age or older.
Undergoing elective complex cardiac surgery (CABG and valve(s) or multiple valves or aortic root, aorta ascendens or aortic arch surgery).
Understood and willingly given written informed consent (Dutch language) to participate following an explanation of study background, restrictions, and procedures.
Experience clinically relevant bleeding of the microvasculature following removal of CPB during surgery (clinically relevant microvascular bleeding defined as a 5-minute bleeding mass between 60 and 250 g)
Intraoperative conditions prior to administration of study medication are:
- Body temperature > 36°C
- Blood pH > 7.3
- Hb > 5.3 mmol/L or Ht > 0.25
- ACT < 140 seconds

Exclusion criteria

•Positive pregnancy test, pregnancy or lactation.
•Women of child-bearing age not using a medically approved method of contraception during the study.
•Undergoing an emergency operation.
•Proof or suspicion of a congenital or acquired coagulation disorder (e.g. VWD or via severe liver disease).
•Myocardial Infarction (MI) or apoplexy in the 2 months preceding study surgery.
•Manifest venous or arterial thrombosis.
•Medication:
-Clopidogrel administration in the 5 days preceding surgery.
-Tirofiban administration in the 2 days preceding surgery.
-INR >1.4 if on coumadines.
•Participation in another clinical study in the 4 weeks preceding this study.
•Sensitivity to any of the components of study medication.
•Any indication that the restrictions or procedures of the study may not be adhered to (e.g.

an uncooperative attitude).
•Any indication that the study restrictions, procedures, or consequences therein have not been considered or understood, such that informed consent cannot be convincingly given.
•Multiple morbidities, with a notably constrained remaining length of life.

Study design

Design

Study phase:	2
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):	23-03-2011
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Haemocomplettan® P
Generic name:	Fibrinogen
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	13-07-2010

Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-08-2010
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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
Other	clinicaltrials.gov ID NCT01124981
EudraCT	EUCTR2009-018086-12-NL
CCMO	NL32188.075.10