Preserved platelet function during cardiopulmonary bypass with aprotinin in dual antiplatelet therapy.

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Primary objectiveTo determine whether aprotinin can reverse the increased postoperative blood loss, induced by dual anti-platelet therapy in elective non-complex cardiac surgery.Secondary objectiveTo determine whether aprotinin reduces transfusion...

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

Summary

ID

NL-OMON49829

Source
ToetsingOnline

Brief title
Aprotinin study

Condition

- Cardiac therapeutic procedures

Synonym
Coronary Artery Bypass Grafting, coronary artery disease, single valve surgery

Research involving
Human

Sponsors and support

Primary sponsor: Isala Klinieken
Source(s) of monetary or material Support: Nordic Pharma;unrestricted grant.

Intervention

Keyword: Aprotinin, Cardiopulmonary bypass, Dual antiplatelet therapy

Outcome measures

Primary outcome

7.1 Primary efficacy endpoint

1. Postoperative blood loss measured as drain production blood loss in ml between chest closure and 12 hours after surgery, or until drain removal if earlier.

Secondary outcome

7.2 Secondary efficacy endpoints

1. Postoperative blood loss, measured as blood loss at the ICU between closure of chest and:

• 1st hour

• 2nd hour

• 3rd hour

• 24th hours

• At the actual time of chest tube removal.

2. Bleeding class defined by the Universal Definition of Postoperative Bleeding 19

3. Number of units of allogenic blood products (platelets + FFP + RBCs) administered to subjects, between administration of study medication and closure of chest

4. Number of units of allogenic blood products (platelets + FFP + RBCs) administered to subjects, between administration of study medication and 24

hours thereafter.

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

6. Number of units of fibrinogen, PCC or Novoseven given in the peri- and postoperative period.

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

8. Ventilation-time in hours during ICU stay.

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

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

11. Proportion of subjects that receive a follow-on surgery to correct unacceptable bleeding within 7 days of last suture.

12. Wound, sternal or other types of infection.

13. Major clinical events:

o Mortality at 30 days post-surgery

o MACE (major adverse cardiac event)

o Cerebrovascular accident/ transient ischemic attack

o Renal failure, defined as need for dialysis therapy

o Venous thromboembolism/ pulmonary embolism

o Allergic or other systemic reaction to study medication

14. Total costs of the procedure are calculated from data generated by the hospital administration and are composed of

o OR time

o Days in the ICU

o Total days in hospital

o Consumption of blood products and hemostatic agents.

o Use of additional medical treatment e.g. dialysis

Study description

Background summary

Dual antiplatelet therapy (DAPT), the combination of aspirin with clopidogrel, has been shown to reduce ischaemic complications in patients presenting with acute coronary syndrome (ACS). 1 ACS patients are often treated with urgent or acute angiography, followed by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). In these patients, long-term clopidogrel + aspirin therapy significantly reduces the risk of adverse ischaemic events. 2 Although the preoperative use of aspirin alone does not affect postoperative bleeding, its use in combination with clopidogrel can be responsible for increased postoperative bleeding, blood products requirement, and need for surgical re-exploration, which in turn may cause a further range of complications. 3,4 Patients undergoing cardiac surgical procedures remain at significant risk of major bleeding and exposure to blood products. Severe bleeding and the need for perioperative transfusion are associated with worse outcomes. Therefore, several blood-sparing strategies showed important decrease in transfusion need of allogenic blood products and have been implemented in addition of prophylactic use of antifibrinolytic agents. 4,5
However, DAPT has drawbacks as patients are prone to bleeding, especially if urgent or acute cardiac surgery is required. It has been confirmed that clopidogrel, in combination with aspirin before CABG, is associated with higher postoperative bleeding and blood product use. 6
The 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation recommend that in patients without signs of recurrent or ongoing ischaemia, CABG should be delayed for 5 days following interruption of ticagrelor or clopidogrel therapy and 7 days following interruption of prasugrel therapy. Aspirin should be continued through surgery except in patients with markedly increased bleeding risk (e.g. redo CABG or complex combined procedures) or in patients who refuse blood transfusion; in such patients it may be advisable to stop aspirin 3-5 days preoperatively. 7
The recent joined EACTA-EACTS guidelines recommend to stop DAPT therapy > 5

days before cardiac surgery and the use of antifibrinolytics tranexamic acid and aprotinin during surgical procedure. 8
Aprotinin has shown to decrease bleeding and the need for transfusion in patients undergoing CABG surgery who continued the use of combined clopidogrel and aspirin within 5 days before surgery. 9-11 A recent prospective study, however, confirmed that, despite the prophylactic use of tranexamic acid, bleeding was increased by 22% in clopidogrel treated patients. 12
Therefore, aprotinin may be preferred over TXA in DAPT treated patients, and recent publications mention DAPT treated patients as target group for the use of aprotinin. 11,13,14
On the other hand, surgical techniques and Patient Blood Management procedures have changed in the past decade. Therefore, the additional benefit of aprotinin over tranexamic acid could be debated.

The risk of bleeding during cardiac surgery depends on the combination of the type of surgical intervention on one hand, and the patient profile on the other hand.
Clinical studies and expert opinion mention patient related independent risk factors like preoperative anemia (Hb< 6mmol/L), low platelet count (<125.000 /mm³), acquired platelet dysfunction (mainly DAPT less then 5 days before surgery), inherited or acquired coagulopathies, female gender, age > 70y and low body weight. Other co-morbidities could include Hypertension, Diabetes mellitus, peripheral vascular disease, renal insufficiency, Asthma, COPD, unstable angina and myocardial infarction (MI).9-15
Meybohm et al published a risk stratification, based on surgical procedure, defined as low risk (predominantly isolated coronary artery bypass graft (CABG) or single valve surgery), medium risk (combined cardiac surgery, e.g. CABG with valve surgery) and high risk (complex surgery, e.g. redo sternotomy, multiple valve surgery, surgery of ascending aorta or aortic arch, or emergency surgery). 16 Also prolonged CPB time and deep hypothermia are recognized as surgical high risk factors. 17
The goal of this pilot study is to verify the effect size of a study investigating the use of aprotinin versus the actual systematic use of tranexamic acid in patients, at dual anti-platelet therapy (high risk of bleeding), undergoing on-pump non-complex cardiac surgery (CABG or single valve) with low risk of bleeding, in a single center prospective cohort.

Study objective

Primary objective
To determine whether aprotinin can reverse the increased postoperative blood loss, induced by dual anti-platelet therapy in elective non-complex cardiac surgery.

Secondary objective
To determine whether aprotinin reduces transfusion of allogenic blood products in patients on dual antiplatelet therapy undergoing simple cardiac surgery and

to determine whether its use is safe and well-tolerated.

Study design

This phase II study is a single-center, investigator initiated, randomized, single-blind controlled study. This study will be conducted in subjects who are undergoing elective complex cardiac surgery. Simple cardiac surgery is defined as CABG or single valve surgery. This study will be performed at a single center in Zwolle, the Netherlands, by the departments of Cardiothoracic Surgery and Cardiothoracic Anesthesia and Intensive Care. The study comprises an intervention group of 29 subjects and a control group of 29 subjects totalling 58 study subjects. Recruitment should require approximately 9 months for the 58 subjects to be enrolled in the study. Baseline examination (including signing of the Informed Consent Document (ICD)) of potential subjects will begin in March 2020 and the data of the last included patient should be completed including follow-up at the end of March 2021 (12 months). Including analysis of the results, the study duration will be approximately 12 months.
Observation of each individual subject will include detailed evaluation from the day of baseline examination (Day *3 to *1) to 30 days post-surgery for SF-36, EuroQoL and SAE recordings. Data for the primary efficacy endpoint will be collected within 24 hours of administration of study medication.

Intervention

6.1 Description of study medication
Aprotinin.
Aprotinine is classified as an antihaemorragic drug subclass, protease inhibitor, ATC-code B02AB01.

Aprotinin is a non-specific serine protease inhibitor with antifibrinolytic properties. By forming reversible stoichiometric enzyme inhibitor complexes aprotinin inhibits human trypsin, plasmin, plasmakallikrein. Aprotinin has a wider therapeutic range compared to tranexamic acid because, besides preventing of formation of plasmin by blocking tPA (tissue plasminogen activator), it also inhibits plasmin directly.
Additionally, aprotinine has beneficial effects when using cardiopulmonaire bypass (CPB), by low intrinsic anticoagulation (inhibition of trombin and thrombin generation by tissuefactor), anti-inflammatory action, reduction of pulmonary and cardiac oxidative stress and the protection against inactivation of platelets, preserving platelet function.

6.2 Summary of findings from clinical studies
Several studies have described the effect of aprotinin compared to tranexamic acid. The estimated effect size in the reduction of postoperative blood loss from a few studies is represented in table 1 (see protocol)

There have been 2 studies describing the effect of aprotinin in dual anti-platelet therapy.9,10 However, these studies were placebo controlled and did not have tranexamic acid in the control group.
A recent meta-analysis compared the safety of aprotinin with tranexamic acid and amino-caproic acid.18 The findings of this analysis are summarized in figure 1.(see protocol)

6.3 Description of route of administration
Aprotinin is administered intravenously, and in the reservoir of the extracorporeal circuit. The estimated extra volume should be taken into account and be corrected for, with regard to total volume balance.

6.4 Description of dosage
After a test dose of 10,000 KIU the remaining loading dose is administered, a total of 1 milj. KIU. Following this loading dose, a continued infusion is given, 250,000 KIU hourly. An additional 1 milj KIU is added to the priming solution of the extracorporeal circuit.

6.5 Preparation and labelling
Aprotinin is stored at room temperature. Under sterile conditions, aprotinin is either administered directly from the vials as a loading dose (intravenously or pump priming solution), or transferred into a sterile 50ml syringe, for continuous infusion.

Study burden and risks

1. There is no extra time burden. Participants complete the same questionaires as other patients.
2. After induction of Anesthesia, 5 ml of blood will be drawn for the verify now test. This is not a routine test and therefore an extra burden.
3. Participants are at risk for side effects of the study medication. These are listed under "Intervention".
4. Patiënts receiving aprotinine have an increased risk on myocardial infarction compared to the standard therapy.

Contacts

Public
Isala Klinieken

Dokter van Heesweg 2
Zwolle 8025 AB
NL
Scientific

Isala Klinieken

Dokter van Heesweg 2
Zwolle 8025 AB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Eighteen years of age or older.
2. Undergoing elective on-pump coronary artery bypass surgery.
3. Use of a combination of aspirin and clopidogrel until at least 3 days prior to surgery

Exclusion criteria

1. Positive pregnancy test, pregnancy or lactation.
2. Women of child-bearing age not using a medically approved method of contraception during the study.
3. Undergoing an emergency operation.
4. Proof or suspicion of a congenital or acquired coagulation disorder (e.g. VWD or via severe liver disease).
5. Apoplexy in the 2 months preceding study surgery.
6. Manifest venous or arterial thrombosis.
7. Medication:
o Tirofiban administration in the 2 days preceding surgery.
o INR >1.4 if on coumadines.
8. Participation in another clinical study in the 4 weeks preceding this study.
9. Having received aprotinin in the last 2 months, in the absence of a IgG antibody test

10. Renal dysfunction, defined as eGFR <45 (mL/min/1.73m2)
11. Sensitivity to any of the components of study medication.
12. Any indication that the restrictions or procedures of the study may not be adhered to (e.g. an uncooperative attitude).
13. Any indication that the study restrictions, procedures, or consequences therein have not been considered or understood, such that informed consent cannot be convincingly given.
14. 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:	Single blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-11-2020
Enrollment:	58
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Trasylol
Generic name:	Aprotinin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-12-2019
Application type:	First submission
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
EudraCT	EUCTR2019-003737-42-NL
CCMO	NL70876.075.19