Postoperative Pericardial Flush, to evaluate the effects of pericardial flush with a crystalloid on blood loss after CABG.

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Objectives of the randomized controlled trialPrimary objective: To determine whether postoperative pericardial flush with a crystalloid can reduce postoperative blood loss by effectively removing contaminated pericardial blood after CABG. The...

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

Summary

ID

NL-OMON44986

Source
ToetsingOnline

Brief title
Postoperative Pericardial Flush (CABG)

Condition

- Cardiac therapeutic procedures

Synonym
blood loss, transfusion requirements

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw Doelmatigheidsonderzoek open ronde 2014 (gehonoreerd op 15-10-2013)

Intervention

Keyword: Blood loss, Cardiac surgery, Flush, Pericardial

Outcome measures

Primary outcome

To determine whether postoperative pericardial flush with a crystalloid can reduce postoperative blood loss by effectively removing contaminated pericardial blood after CABG. The primary study endpoints include: blood loss 12h postoperative and delta haemoglobin (between sternal closure and 12h postoperative).

Secondary outcome

All secondary study parameters are derived from standard patient monitoring data; therefore no extra provisions are needed.

ICU

- GENERAL: aBP, dBP, patient rectal/core temperature (°C), mechanical ventilation duration (hours), bairhugger use (hours), removal of chest tubes (hours postoperative), ICU stay (days).
- TRANSFUSION: pumpblood (mL), RBC, platelets (units), plasma (units), fibrinogen (mg), cofact (IE) , novo7 (ml);
- LAB: CRP, leukocytes, pH, platelets, INR, haemoglobin (T24), haemotocrit, CKMB;
- ECG: AF, VT/VF, SVT, AV-Blok, >QRS, MI;

- MEDICATION: AF conversion medication, AF conversion success, antibiotics;

- COMPLICATIONS: early (<48hours) mortality, prolonged mechanical ventilation, infection, atrial arrhythmias, surgical re-exploration, sternal wound infection.

THORACIC SURGERY WARD

- GENERAL: thoracic surgery ward stay (days);

- TRANSFUSION: pumpblood (mL), platelets (units), plasma (units), fibrinogen (mg), cofact (IE), novo7 (ml);

- MEDICATION: AF conversion medication, AF conversion success, antibiotics;

- COMPLICATIONS: generalized infection, atrial arrhythmias, surgical re-exploration, sternal wound infection, in hospital mortality.

DISCHARGE

- Total hospitalization (days);

- LAB: haemoglobin level (Hb);

- X-RAY: pericardial effusion, pleural effusion;

- ECHO: right ventricular function (RVF, tapse), pericardial effusion (mm), LVF.

6 MONTH FOLLOW-UP

- ECHO: right ventricular function (RVF, tapse);

- COMPLICATIONS: late cardiac tamponade, generalized infection, atrial arrhythmias, surgical re-exploration, sternal wound infection; 30-day mortality; late mortality (within follow-up period).

- Graft patency.

- Quality of life (EQ-5D+)

- Health and Labour Questionnaire (SF-HLQ).

- Direct medical costs and indirect costs: the direct medical costs in this study include the costs of all procedures associated with the standard and the experimental intervention. Health care utilization, as described above, will be extracted from hospital databases, case record forms and patient files. Productivity losses will be estimated based on data concerning absence from work (Health and Labour Questionnaire, SF-HLQ).

Substudy parameters/endpoints:

Difference in inflammatory markers (IL-1, IL-6, IL-8, TNF-a, MCP-1, CRP, leukocytes, monocytes, fibrinogen, D-dimeer, albumin, Na, Cl, TF, and tPA) between sternal closure and 12h postoperative. All of the aforementioned parameters will be analyzed in systemic and pericardial blood on timepoints: T-4, T-3, T-2, T-1, T0, and T12. See paragraph 7.1.2. of the study protocol.

Study description

Background summary

This innovative prospective research project has to deliver the world*s first proof of concept for the use of postoperative pericardial flush (PPF). Continuous postoperative flushing of the pericardial cavity has never been described and is essentially innovative. PPF has the potential to develop into a versatile technique to control the pericardial environment; making cardiac surgery procedures cleaner en safer. A reduction of common major complications such as postoperative bleeding, atrial fibrillation and infection will lead to a decrease of RBC transfusions and surgical re-exploration which are

independent risk factors for increased sternal wound infections, transfusion-related complications and higher overall societal costs. When proven (cost-)effective, PPF needs to be integrated into the standard postoperative protocol for all cardiac surgical procedures, allowing it to be used on a very large (global) scale in standard care. The primary clinical goal is to reduce postoperative bleeding and decrease transfusion requirements. Secondly, by reducing postoperative atrial fibrillation and preserving right ventricular function improved patient outcomes may be expected.

Population
Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the world; in the Netherlands accounting for 39.735 annual in 2010, of which 18.581 (46.8%) men and 21.154 (53.2%) female. The proportion of CVD in the overall mortality in 2010 between the ages of 0-54 was 14% (622 deaths) in women vs. 19% (1151 deaths) in men. The proportion of CVD in the total mortality above the age of 85 is 37% (11,303 deaths) in women and 34% (5,163 deaths) in men. [C] Within the group of CVD the majority of mortality is caused by ischemic heart disease and stroke: 47% in women and 51% amongst men. Besides ischemic heart disease and stroke (including cerebral infarction and cerebral hemorrhage) the category 'other heart disease' (which includes heart failure and atrial fibrillation) is a major contributor to mortality in CVD. In 2010 atrial fibrillation accounted for 3.2% of total CVD mortality with a surprising 1:2 ratio between women and men [C]. The intended study results will benefit an increasing population. Over the last 15 years the number of open heart surgeries performed yearly in The Netherlands has increased from 13.327 (1995) to 16.128 (2009) (1107 and 1245 per million respectively). It is expected that the number of open-heart surgery in 2020 will increase further to 18.420; which might be an underestimation of the true increase. There are two important factors that this assessment has not taken into account: an increase in the number of valve and coronary bypass surgeries (CABG) on the basis of increasing life expectancy and changes in indication for operation. [A,B] The expected estimation of the number of open-heart surgeries in 2020 is therefore an underestimation of the true number.

Blood loss and (pericardial) blood
Excessive postoperative blood loss (>2L/24 hours or >200 mL/hour) is one of the most common complications of cardiac surgery. Predictive factors for hemorrhage and reoperation/re-exploration following cardiac surgery include: age, obesity, renal insufficiency, cardiopulmonary bypass (CPB) time and intracardiac repair. Reoperation/re-exploration for bleeding is a strong independent risk factor for adverse outcome following cardiac surgery. Specifically, operative mortality, prolonged mechanical ventilation, acute respiratory distress syndrome, sepsis, and atrial arrhythmias are increased in these patients. In addition, postoperative bleeding requiring multiple transfusions and surgical re-exploration is associated increased sternal wound infection, transfusion-related infection and higher costs [1, 48]. A surgical cause of bleeding is only found in half of patients undergoing

reoperation/re-exploration for bleeding. In the remainder of patients the cause is multifactorial and probably an acquired/surgical related hemostatic defect is responsible for diffuse mediastinal hemorrhage [1].
It is clear that during the first hours after cardiac surgery, clotting is suboptimal while a large internal wound remains. Although strongly fixed together, the two sternal halves are considered an important focus of postoperative bleeding. The normal amount of blood loss after cardiac surgery varies between 300 and 1500 mL during the first 12 hours. To evacuate blood from the pericardial-, and if necessary pleural cavities, chest tubes are left postoperative. However, when blood loss is excessive or when cloths start to develop more rapidly, the drains often fail in their function to evacuate all accumulated blood. Stasis of blood and cloths in the pericardial (and/or pleural) cavity leads to high fibrinolytic activity, maintenance of blood loss and in some cases to cardiac tamponade [2-6].
After removal of the chest tubes, often one day postoperatively, some blood and cloths remain in the pericardial cavity. During the next days, under the influence of fibrinolysis and hemolysis, a highly osmotic liquid solution with high concentration of large molecular proteins (haemoglobin) is formed. This osmotic active solution is known to contribute to the increase of pericardial effusions and late cardiac tamponade in the first weeks postoperatively. The blood and cloths that remain in the pericardial cavity can also induce an inflammatory reaction that may play a role in the decline of right ventricular function, the occurrence of atrial fibrillation and the formation of adhesions [9-11, 46]. Besides directly causing patient discomfort and leading to hemodynamic compromise, postoperative atrial fibrillation is associated with worse clinical outcome regarding mortality, morbidity and costs [2-18].
During redo surgery for postoperative bleeding or tamponade, removal of blood and cloths and flushing the pericardial cavity with warm saline is enough to stop the bleeding immediately in a vast majority of patients. Reoperation for bleeding is a strong independent risk factor for adverse outcome following cardiac surgery. Specifically, operative mortality, prolonged mechanical ventilation, acute respiratory distress syndrome, sepsis, and atrial arrhythmias are increased in these patients. Controlling and stopping the bleeding early postoperatively also means that anticoagulation therapy can be started earlier; reducing the risk of thromboembolic events on the ICU.

Transfusion requirements
In addition, postoperative bleeding requiring multiple transfusions and surgical re-exploration is associated with increased sternal wound infection and transfusion-associated lung injury [7]. The incidence of blood transfusions in cardiac surgery have been reported to vary from 27% to 90% [8]. It has been pursued with the assumption that transfusing an anemic patient will improve the outcome. Blood transfusion has a clearly defined role in the management of hemorrhagic shock and is presumably beneficial in situations where a critically low hematocrit is contributing to a state of oxygen-supply dependency. A number of studies have demonstrated that low hemoglobin (Hb) concentrations and decreased oxygen delivery increase mortality [19,20]. Defoe et al. [21] found

that patients who had a lower hematocrit during CABG surgery were associated with a higher risk of in-hospital mortality [21]. The potential benefits are, however, countered by many transfusion-associated complications: the risk of transfusion-associated lung injury [7], transfusion associated immunomodulation [22], transfusion-related circulatory overload [23], and cellular hypoxia [24]. Blood transfusions have also been linked to postoperative renal dysfunction [25], pneumonia [26], wound infections [27] and severe sepsis [28].
There have been several recent well-designed randomized control trials in critically ill or CABG patients showing a significant association of transfusion with increased short- and long-term postoperative mortality of 66% [29]; morbidity [30,31] and healthcare costs [32]. Different studies showed that lower Hb and Ht levels increase mortality as well [19-21]. The short-term adverse effects of blood transfusion in cardiac surgical patients are well documented but there are few studies conducted assessing long-term survival [29,33-35]. Others [36] stated that bleeding, increased chest tube production, is associated with higher mortality through mechanisms not related to blood transfusion. Despite all the available evidence, the transfusion practices vary substantially [8,38]. Efforts made to decrease transfusion rates in cardiac surgery show persistent effects for several years [39]. The use of blood and other blood product transfusion in cardiac surgical patients still remains very high. Adult cardiac surgery utilizes a significant proportion of all packed red blood cell (PRBC) transfusions all over the world. The incidence of blood transfusion in patients undergoing cardiac surgery has been reported to vary from 27% to 90% [8]. Transfusion of a single RBC unit may increase the direct medical costs due to hospitalization with 10% [40].

Atrial fibrillation

Besides directly causing patient discomfort and leading to hemodynamic compromise, several studies have demonstrated that post-operative atrial fibrillation (AF) is associated with: an increased risk of postoperative stroke, represented by an annual stroke rate of 5% in patients with AF [12-14]; a higher rate of in-hospital mortality (5.8% vs. 2.2%, P=0.003) [12]; longer intensive care unit and hospital stays [12,13,15,16,41] and higher costs of treatment [17,18]. Both paroxysmal and chronic AF have shown a significant increase of the risk of stroke, especially in older patients [42].

Right ventricular function

In CABG, right ventricular function is impaired directly postoperatively and recovers to preoperative state levels within six months [49]. Various hypotheses regarding the pathogenesis of the selective decline in RVF after cardiac surgery have been put forward. However, no clear cause has been found. It is possible that the thin-walled right ventricle may be more susceptible to dysfunction secondary to inflammation or effusions postoperatively [50]. These effusions may result from local tissue damage or from a systemic inflammatory response. Another theory suggests that postoperative pericardial adhesions may impair right ventricle filling. Prospective studies are needed to elucidate this phenomenon.

Rationale
We believe that the occurrence of all previous outlined postoperative complications is influenced by a common denominator that we consider to be a pericardial cavity contaminated with blood. We hypothesize that a new therapeutic technique, continuous postoperative flushing of the pericardial cavity with saline (Postoperative Pericardial Flush) can contribute to a cleaner pericardial space; hereby reducing postoperative blood loss, transfusion requirements, atrial fibrillation, inflammatory response and infection, and postoperative right ventricular function impairment. This will improve clinical outcome with respect to mortality and morbidity, increase HRQoL post cardiac surgery and decrease societal health-care costs.

Study objective

Objectives of the randomized controlled trial
Primary objective:
To determine whether postoperative pericardial flush with a crystalloid can reduce postoperative blood loss by effectively removing contaminated pericardial blood after CABG. The primary study endpoints include: blood loss 12h postoperative and delta haemoglobin (between sternal closure and 12h postoperative).

Secondary objectives:
To determine the effect of postoperative pericardial flush on:
- RBC transfusion (After randomization);
- In-hospital complications (Operative mortality, mortality, prolonged mechanical ventilation, infection, atrial arrhythmias, surgical re-exploration, sternal wound infection);
- Haemoglobin levels at discharge;
- ICU stay and total hospitalization duration;
- Adverse effects within the follow-up period of 6 months (Late cardiac tamponade, infection, 30-day mortality; mortality within the follow-up period);
- Right ventricular function (6 months follow-up);
- Health related quality of life (HRQoL using EQ-5D+ at 6 months follow-up);
- Cost-effectiveness (Compared by assessing cost per quality adjusted life year (QALY), calculated from the health utility gain scores obtained with the EQ-5D+ questionnaire. Costs are divided in direct medical costs, consisting of hospital days, ICU-days, medication, transfusion requirements, costs related with in-hospital complications and indirect costs).

Objectives of the substudy
Primary objective:
To determine whether postoperative pericardial flush with a crystalloid can reduce postoperative intrapericardial and systemic inflammatory response. The primary study endpoints of the substudy include: difference in inflammatory markers (IL-1, IL-6, IL-8, TNF-a, MCP-1, CRP, leukocytes, monocytes,

fibrinogen, D-Dimeer, albumin, Na, Cl, TF, and tPA) between sternal closure and 12h postoperative.

Study design

This study is designed as a prospective single-blind randomized trial with evaluation of patient outcomes after a clinical follow-up of six months. Patients are included consecutively within the AMC.

This study is supported by ZonMw within the *Doelmatigheidsonderzoek 2013-2015* program for which approval was obtained on 15-10-2013. After re-approval of the MERC this study will start a preparation period of 1 month (December 2013) before the first patient is included. Our aim is to include 3 CABG patients a week; patients are operated on Mondays, Tuesdays and Fridays. Inclusion of all 170 patients will take 12 months. Data analysis will be performed as soon as the last patient has had his 6-month follow-up; data analysis will take 4-6 months.

Intervention

Postoperative Pericardial Flush (PPF) system
The PPF system is aimed to extract the contaminated pericardial blood, dilute thrombi, decrease postoperative blood loss, and prevent the formation of postoperative pericardial adhesions via dilution and rotation of the fluid stream. The perfusion fluid, NaCl 0,9%, has minor or no effects on the pericardial tissue, haemostatic and fluid balance of the patient, but dilutes possible thrombi. The pericardial inflow Redon drain will be inserted through a small extra incision that is similar to the incision for the standard chest tubes. This extra incision is needed because previous studies (safety and feasibility study and a currently ongoing randomized trial in CHD patients) have shown that leakage of the flushing fluid might occur when the inflow drain is inserted through the same incision as one of the standard incisions for the chest tubes. If necessary, a separate drainage tube will be inserted into the pleural cavity. Every opened (pleural/pericardial) cavity is drained separately. The outflow tract is a closed low vacuum drain collection system, draining the pericardial cavity under low / negative pressure of 15cmH2O and with a total volume of 2000mL. If required, fluid replacement or blood transfusion will be given.

PPF will be performed continuously after operation, starting from the moment the sternum is closed (T-1) until the total flushing volume of 7000ml has been completely infused. After the Pericardial Flush system has stopped approximately 14 hours post T-1, the system will be disconnected from the inflow Redon drain. In the case of persistent blood loss after disconnection of the PPF system, standard ICU thoracic drain protocol will be respected.

Implementation of the PPF system is standardized on a previous safety and feasibility trial that was performed at our institution and on a similar randomized clinical trial (in patients with congenital heart disease) which is currently beeing performed at our institution (NL42595.018.12). PPF flow rate (inflow) and thoracic drain production (outflow) are double monitored. Primary, data is entered into a specially designed and integrated input field in the ICU*s PDMS, which is done hourly by ICU staff. PDMS automatically calculates the net thoracic drain production. Secondary, the VTBI is checked on the infusion pump by a research nurse after 1h, 3h, 6h, 12h and 24h; the same is done for thoracic drain production. Flow rate adjustments are made in the event of fluid accumulation and or total drain obstruction. In the event of >200ml fluid accumulation the PPF flow rate will be lowered to 100mL/hour and if not evacuated during the next two hours, the PPF system will be stopped. In the event of total thoracic drain / outflow tract obstruction the PPF will be stopped until the obstructed chest tube(s) are functional again. During the whole course of the experiment the patients* hemodynamics are monitored extensively by continuous arterial and central venous line measurements according to standard intensive care unit protocols. Routinely much attention is given to signs of fluid accumulation in pericardial and/or pleural cavities. When indicated chest X-ray or echocardiography will be performed to evaluate fluid retention in pleural space and/or pericardial cavity. If required, fluid replacement or blood transfusion will be given.

Inflow tract:
- NaCl 0,9% (7000ml via standard infusion line);
- Volumetric pump (flow rate of: 500mL/hour);
- Enflow® Blood and Fluid warming system;
- Perforated silicon drain.

Outflow tract:
- Perforated silicon drain (MEDICA Europe) 30Ch (CE0344);
- Standard low vacuum drain collection system.

Time points 6 months follow-up
T-D = One day preoperative;
T-4 = Baseline before induction of anesthesia;
T-3 = Before institution of CPB;
T-2 = After discontinuation of CPB;
T-1 = Closure sternum / start Pericardial Flush system (infusion of 7000ml at a constant flow rate of 500ml/h);
T0 = ICU arrival;
T6 = ICU arrival + 6 hours;
T12 = ICU arrival + 12 hours;
(stop of the Pericardial Flush System after 14 hours);
T24 = ICU arrival + 24 hours.
TW = Arrival on thoracic surgery ward
T+D = Discharge from hospital

T+6M = 6 months follow-up

Additional blood samples
Additional blood samples on top of those needed for regular treatment will be collected at six timepoints, as shown in Figure 3 of the study protocol. All bloos samples from the systemic circulation will be drawn from the central artery line that is part of the regular treatment. Sampling by itself will therefore not be an extra burden for the patient. Extra samples include: blood samples from the central artery line (intra- en postoperative), samples of pericardial blood (intraoperative), and samples of mediastinal chest tube drainage fluid (postoperative). Extra systemic blood samples will be collected at the same moment and following blood samples that are needed for standard treatment. Timepoints: before induction of anesthesia (1xEDTA and 1xCitrate from the systemic circulation), before institution of CPB (1xEDTA and 1xCitrate from the systemic circulation), after discontinuation of CPB (1xEDTA and 1xCitrate from the systemic circulation and 2 samples of pericardial blood), before sternal closure (1xEDTA and 1xCitrate from the systemic circulation and 2 samples of pericardial blood), Arrival on ICU (1xEDTA and 1xCitrate from the systemic circulation and 2 samples of mediastinal chest tube drainage), 12 hours after ICU arrival (1xEDTA and 1xCitrate from the systemic circulation and 2 samples of mediastinal chest tube drainage). Total samples per patient needed: blood samples from central venous line (12), samples of pericardial blood (4), samples of mediastinal chest tube drainage fluid (4). The following markers will be determined per sample IL-1, IL-6, IL-8, TNF-a, MCP-1, CRP, leukocytes, monocytes, fibrinogen, D-dimeer, albumin, Na, Cl, TF, and tPA. Blood samples will be put into centrifuge directly after collection. Plasma will then be distributes over 5 smaller samples. All samples will be labelled and stored in a freezer at -80°C.

Study burden and risks

The development of expected adverse events, infection and fluid retention (in pleural and pericardial cavities), will be closely monitored via several imaging techniques and laboratory measurements. The blood samples necessary for the study are not expected to negatively influence the result of treatment. A possible benefit for a patient receiving the pericardial perfusion might be active (central) warming when a patient suffers from hypothermia.

Adverse Events (AE)
An adverse event (AE) is defined as any undesirable experience occurring to a subject during this trial, whether or not considered related to postoperative pericardial flush. The difference between adverse events and serious adverse events is that AE does not result in events as described in the section serious adverse events. All adverse events observed by the investigator or his staff will be recorded in the eCRF by the investigator.

Serious Adverse Events (SAEs)

This study population has a high risk of serious complications, which are inherent to their vulnerable condition and unrelated to postoperative pericardial flush, which is under evaluation in this trial. Complications are included in the primary and secondary outcomes of this study and are recorded in the Case Report Form (eCRF). All SAE*s are reported to the DSMB every 6 months during the 2 year study period. SAE*s that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

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

- All adult patients (>18y) undergoing surgery for CABG.

Exclusion criteria

- Previous CABG;
- Emergency surgery;
- Preoperative use of Dabigatran, Rivaroxaban, Apixaban, Clopidogrel, Brilique or Prasugrel;
- Participation in any study involving an investigational drug or device;
- Age <18 years and/or inability to understand study information / give informed consent.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-01-2014
Enrollment:	180
Type:	Actual

Medical products/devices used

Generic name:	Drain
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	17-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24893
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL43190.018.13
OMON	NL-OMON24893