HEMOSTASIS AND TRANSFUSION IN CARDIAC SURGERY

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INTRODUCTION

Bleeding is an important issue in cardiothoracic surgery.

20% of all blood products are transfused in this clinical setting worldwide.

More than 25% of allogeneic blood transfusions have been considered inappropriate.

Both bleeding and allogeneic blood transfusion are associated with increased morbidity, mortality, and hospital costs.
The risk of bleeding and reoperation

THE CARDIAC SURGERY PATIENT

HEMOSTATIC ABNORMALITIES IN THE CARDIAC SURGICAL PATIENT

Management of the patient taking preoperative antithrombotic drugs
Abnormalities acquired during cardiac surgery

ANTICOAGULATION FOR CPB
POINT OF CARE COAGULATION TEST
ASSESSMENT OF POTENTIAL BLEEDING RISK
PHARMACOLOGICAL AGENTS
PERIOPERATIVE STRATEGY, MULTIMODAL APPROACH
PERIOPERATIVE BLEEDING GUIDELINES (ESA)
Management of the patient taking preoperative antiplatelet drugs

Recommendations

Withdrawal of aspirin therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. A

Withdrawal of clopidogrel therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. A
The multiple electrode aggregometry (MEA) ADP test in patients under thienopyridine (ticlopidine or clopidogrel) undergoing cardiac surgery is associated with postoperative bleeding and platelets transfusion. MEA provides an accurate preoperative prediction of postoperative bleeding.

<table>
<thead>
<tr>
<th>test</th>
<th>activation</th>
<th>sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPItest</td>
<td>arachidonic acid: is converted to TXA2 by platelet-own cyclooxygenase</td>
<td>aspirin, IIb/IIIa antagonists</td>
</tr>
<tr>
<td>ADPtest</td>
<td>ADP: binds onto platelet ADP receptors</td>
<td>clopidogrel, IIb/IIIa antagonists</td>
</tr>
<tr>
<td>ADPtest HS</td>
<td>ADP + prostaglandin E1 (Prostaglandin is a natural inhibitor and enhances the sensitivity of the assay for clopidogrel)</td>
<td>clopidogrel, IIb/IIIa antagonists</td>
</tr>
<tr>
<td>TRAPtest</td>
<td>TRAP-6 (thrombin receptor activating peptide): TRAP-6 is a potent agonist which mimicks the platelet-activating action of thrombin</td>
<td>Ilb/IIIa antagonists</td>
</tr>
</tbody>
</table>

**GpIIb/IIIa antagonists:**
- Reopro ® (abciximab)
- Aggrastat ® (Tirofiban)
- Integrillin ® (Eptifibatid)
no platelet inhibition

100 mg aspirin qd

75 mg clopidogrel qd

100 mg aspirin + 75 mg clopidogrel qd

NORMAL RANGE: …

► Multiplate tests
Management of the patient taking preoperative anticoagulant drugs

Vitamin K antagonist

We recommend bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADSS2 score >2, pts with recurrent VTE treated for <3 months, pts with mechanical valve). Day 5: last VKA dose; DAY 4: no heparin; Days 2 and 3: therapeutic subcutaneous LMWH twice daily or subcutaneous UFH, Day 1: hospitalization and INR measurements. Day 0: surgery.

1C

We recommend that, in VKA treated pts undergoing procedure or developing a bleeding complication, PCC (25 IU FIX/kg) should be given.

1B

Dabigatran and rivaroxaban
In case of severe haemorrhage in a critical organ, it is proposed to reduce the effect of anticoagulant therapy using a nonspecific procoagulant drug (activated prothrombin concentrate, FEIBA, 30-50U/kg, or non-activated 4-factors prothrombin concentrates 50U/kg).

Abnormalities acquired during cardiac surgery with cardiopulmonary bypass

1. Hemodilution
2. Contact System
3. Fibrinolytic System
4. Inflammation
5. Platelets  
   *thrombocytopenia*
   *platelets dysfunction*
Effect of hemodilution on stable factor levels.

Priming fluid reduces all factors in blood including coagulation factors, inhibitors, and activation markers, by approximately 30% to 40%.

Contact activation

Patient Vascular System

Bypass Circuit

Activated Blood

Venous Reservoir
Conventional CPB leads to substantial increases in thrombin activation markers, unrelated to the surgical wound itself.

Platelets activation – aggregation - release granule contents.

Major platelet receptor-ligand interaction

- PAR-1
- PAR-4
- Thrombin
- VWF
- GPIb/IX/V
- GPVI
- α₂β₁
- α₂A
- ADP
- P2Y₁
- P2Y₁₂
- α₂₅β₃

Protamine
Heparin

- Plasmin
- GPIIb/IIIa
REDUCING ACTIVATION

Limiting Use of Cardiotomy Suction
Increasing Circuit Biocompatibility
Decreasing CPB Circuit Size
Off-Pump Coronary Artery Bypass

**Heparin** – suppress thrombin activation

**Antifibrinolytics**

- Tranexamic acid during CPB preserves platelet adenosine diphosphate levels
- Aprotinin during CPB reduces platelet activation, preserves PAR1 function, and reduces platelet GPIb cleavage.
ANTICOAGULATION FOR CPB

Large doses of heparin
Heparin resistance
Insufficient heparin

Unneutralized heparin
Heparin rebound
Protamine overdose

Heparin and Protamine Dosing

Bleeding diathesis
FFP as an alternative to AT concentrate - 2 U FFP = 500 IU AT

POINT OF CARE COAGULATION TEST (POC)

Results must be timely as well as accurate

Bedside test utilize whole blood samples

Analysis the coagulation in its entire
1. Functional measures of coagulation or test that measures the intrinsic coagulation pathway
   - Activating Clotting Time (ACT)
   - High-dose thrombin time (HiTT)
2. Heparin Concentration Monitors + ACT
   - Protamine titration method
3. Viscoelastic measures of coagulation (TEG, ROTEM)
4. Platelet function monitors
Thromboelastometry (ROTEM)

(a) 10 min

- Maximum amplitude (mm) (MA) = Maximum clot firmness (MCF)
- Fibrinolysis [%]:
  - Clot lysis index (CLI-30; CLI-60)
  - Maximum lysis (mL)
- Reaction time (t) = Coagulation time (CT) (sec)
- Coagulation time (k) = Clot formation time (CFT) (sec)

(b)

- Normal
  - (CT;CFT;MCF)
  - α-angle normal
- Hyperfibrinolysis
  - (CT;CFT normal or prolonged)
- Platelet or fibrinogen depletion
  - (CFT prolonged; MCF) reduced; (α-angle reduced)
- Heparin or Factor deficiency
  - (CT;CFT prolonged; MCF; α-angle reduced)

Assessment of potential bleeding risk

A structured patient interview or questionnaire before surgery or invasive procedures

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery

1C
Predictors of postoperative bleeding

1. Advanced age (age > 70 years)
2. Small body size or preoperative anemia (low RBC volume)
3. Anti-platelet & anti-thrombotic drugs
4. Prolonged operation (CPB time)
5. Emergency operation or complex operation
6. Other co-morbidities (CHF, COPD, HTN, PVD, renal failure)

Pharmacological agents

Antifibrinolytic therapy
- tranexamic acid and EACA
- aprotinin

Fibrinogen concentrate
Prothrombin complex concentrate (PCC)
Desmopressine (DDAVP)
Recombinant activated factor VII (rFVIIa)
Factor XIII concentrate
The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery.

- retrospective single-center cohort study (2000-2008)
- 15,365 patients
- cardiac surgery with cardiopulmonary bypass
- aprotinin [6 x 10(6) U] or tranexamic acid (50-100 mg/kg)

Aprotinin tends to have a better risk-benefit profile than tranexamic acid in high-risk, but not low- to moderate-risk, patients. Its use in high-risk cases may therefore be warranted.

Karkouti K, et al
We recommend that intraoperative tranexamic acid or EACA administration should be considered to reduce perioperative bleeding in high, medium and lower risk cardiovascular surgery.  

We recommend the consideration of tranexamic acid (20-25 mg/kg).
We recommend plasma fibrinogen level <1.5–2.0 g/l⁻¹ or ROTEM/TEG signs of functional fibrinogen deficit as triggers for fibrinogen substitution.

1C

We recommend that fibrinogen concentrate infusion guided by point of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiac surgery.

1B

We suggest an initial fibrinogen concentrate dose of 25-50 mg/kg⁻¹

2C
We suggest that PCC (20-30 IU/kg) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients.

2C
Low levels of endogenous ATIII

PCC 4
Protein C
Protein S
ATIII
Protein Z
We suggest that off-label administration of rFVIIa can be considered for bleeding which cannot be stopped by conventional, surgical or interventional radiological and/or when comprehensive coagulation therapy fails.

2C

Hypofibrinogenaemia, thrombocytopenia, hypothermia, acidosis and hyperfibrinolysis should be treated before rFVIIa.
# Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

## Table 3. Arterial Thromboembolic Events with a Rate Greater Than 0.5%.

<table>
<thead>
<tr>
<th>Variable</th>
<th>rFVIIa (N=2583)</th>
<th>Placebo (N=1536)</th>
<th>Odds Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All arterial thromboembolic events</td>
<td>141 (5.5)</td>
<td>49 (3.2)</td>
<td>1.68 (1.20–2.36)</td>
<td>0.003</td>
</tr>
<tr>
<td>Coronary events</td>
<td>76 (2.9)</td>
<td>17 (1.1)</td>
<td>2.39 (1.39–4.09)</td>
<td>0.002</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>57 (2.2)</td>
<td>11 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased troponin level</td>
<td>19 (0.7)</td>
<td>6 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>45 (1.7)</td>
<td>20 (1.3)</td>
<td>1.27 (0.74–2.17)</td>
<td>0.39</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>44 (1.7)</td>
<td>19 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis†</td>
<td>1 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intra-operative strategy clinical judgment ??
Intra-operative strategy
multimodal approach
Reoperation causes

18,891 primary and repeat
1. coronary artery bypass grafting
2. valve
3. combined operations

Risk factors included:
• older age
• greater comorbidity
• aortic valve surgery
• longer myocardial ischemic durations
• surgeon.

3.0% underwent reoperation for bleeding
Reoperation causes
• technical factors (74%),
• coagulopathy (13%),
• both (10%)
• other (3.3%)

Cell-savage

Centrifugation of pump-salvaged blood, instead of direct infusion, is reasonable for minimizing post-CPB allogeneic red blood cell (RBC) transfusion. IIa (A)

Ultrafiltration

Use of modified ultrafiltration is indicated for blood conservation and reducing postoperative blood loss in adult and pediatric cardiac operations using CPB 1A

Benefit of the use of conventional or zero balance ultrafiltration is not well established for blood conservation and reducing postoperative blood loss in adult cardiac operations. IIb (A)

2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines

Ferraris A Ann of Thorac Surgery; 2011;91:944-82
Management of hemorrhage in cardiothoracic surgery.

Individualized goal-directed hemostatic therapy ("theranostic" approach)

POC transfusion and coagulation management algorithms

**guided** by

1. viscoelastic tests: TEG/ROTEM
2. POC platelet function tests:
   whole blood impedance aggregometry (MEA)

**based** on first-line therapy with fibrinogen and prothrombin complex concentrate.

First-line therapy with coagulation factor concentrates combined with POC coagulation testing

Retrospective study - 3,865 pts. in cardiac surgery
High risk of bleeding or clinically relevant diffuse bleeding after protamine

♦ Decreased incidence of:
  1. Blood transfusion
  2. Thrombotic/thromboembolic events
  3. Reexploration

♦ Overall costs for allogeneic blood transfusion and factor concentrates per patient decreased by 6.5%.
Haemostatic therapy algorithms with POC testing reduced:
1. the number transfused units of RBC, FFP, PC
2. costs of therapy

First study showing improved survival!
Principles of the POC - supported coagulation management algorithm

- rFVIIa
- FXIII
- Platelets
- 4F-PCC (or FFP)
- Fibrinogen (or Cryo)
- Antifibrinolytics
- Aspirin? Oral anticoagulants? Heparin?
- Basic conditions
  - $T_c > 34^\circ C$; $pH > 7.2$; $Ca_i > 1$ mmol/l; $Hb > 8$ g/L
- Surgical stanching
  - (Compression bandage; pelvic compression; packing)

Görlinger, 2012
ROTEM-based Point-of-Care Coagulation Management in Patients with Acute Aortic Dissection

Retrospective study
Surgery for Acute type A aortic dissection
January to December 2012.
The same team of surgeons
Two different peri operative haemostatic therapies

1. ROTEM-based Point-of-Care coagulation management-ROTEM group- RG
2. Usual care (standard) – UCG group

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Bucharest, Romania
Declamping of the Aorta

ROTEM

MCF FIB < 5 mm

Yes

Fibrinogen ????

Cryoprecipitate
10-15UI

Before Protamine

No

A10 Ex < 30 mm
and
A10 FIB > 6 mm

Yes

Order of PC

No

Optimize before weaning from CPB:
Temp > 36°, pH > 7.2
Ca i > 1mmol/l, Hb > 8g/dl

Yes

Protamine

Diffuse bleeding after protamine
Repeat ROTEM after each intervention

CT IN > 240 sec
CT HEP/CT IN < 0.8

No

A10 EX ≤ 40mm and A10 FIB ≤ 10mm

Yes

Cryoprecipitate 10-15 UI

Fibrinogen ???

No

CT EX > 90 sec or CT HEP > 280 sec

Yes

PCC 20-40 UI/kg or FFP 15 ml/kg

No

A10 EX ≤ 40mm or A10 FIB > 10mm

Yes

Transfusion of PC

MEA ???

No

CT EX < 80 sec A10 EX > 15mm or A10 FIB > 50mm

Yes

Active rewarming or NaHCO3, CaCl2, PCC, FFP, PC, PRBC

No

FFP Cryoprecipitate
Result (5)

Allogenic blood product exposure

<table>
<thead>
<tr>
<th></th>
<th>RG</th>
<th>UCG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values:
- PRBC: P=0.038
- PC: P=0.042
- FFP: P=0.075
- CP: P=0.317
- Total: P=0.021
Use of standardised haemostatic algorithms with intervention triggers measured using thrombelastography or thromboelastometry at the point-of-care may reduce transfusion requirements and perioperative blood loss in cardiovascular surgery.
Thank you!
GUIDELINES

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Sibylle A. Kozek-Langenecker, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa Alvarez Santullano, Edoardo De Robertis, Daniela C. Filipescu, Dietmar Fries, Klaus Görlinger, Thorsten Haas, Georgina Imberger, Matthias Jacob, Marcus Lancé, Juan Llau, Sue Mallett, Jens Meier, Niels Rahe-Meyer, Charles Marc Samama, Andrew Smith, Cristina Solomon, Philippe Van der Linden, Anne Juul Wikkelsø, Patrick Wouters and Piet Wyffels
TRAPtest

GpIIb/IIIa antagonists:
Reopro® (abciximab)
Aggrastat® (Tirofiban)
Integrillin® (Eptifibatid)

ADPtest

Aspirin®
NSAID

Activated platelet

platelet activation
GpIIb /IIIa receptor exposure
degranulation

resting platelet

Multiplate tests

Clopidogrel
Prasugrel
Cangrelor

P2Y12

TRAP

ADP

Arachidonic Acid

COX

ArA1

TXA2

COLtest

Collagen

AsPItest

Arachidonic Acid

Aspirin®

NSAID

PGE1

ADPtest HS

(ADP + PGE1)
Normal hemostasis

1. Platelets
   Initial Plug

2. Coagulation
   Clot Stabilization

3. Endothelium
   Inhibitors, Regulation

4. Fibrinolysis
   Clot Size Control

WOUND
Prothrombin complex concentrate

Rapid reversal of coumarin effect
Patients with defective hepatic synthesis of coagulation factors
Improvement of coagulation in patients with massive blood loss
Patients with factor II or X inherited defects
Recombinant factor VIIa (rFVIIa)

Licensed only for use in:
- hemophiliacs with inhibitors to factor VIII or IX
- acquired hemophilia
- FVII deficiency
- Glanzmann thrombastenia
- refractory to platelets

Off-label use of rFVIIa
- Trauma
- Abdominal surgery
- Thoracic surgery
- Orthopedic surgery
- Hepatic procedures
- Cardiac surgery
- Non-surgical bleeding
- Acquired coagulopathies
- Obstetric hemorrhages
rFVIIa: efficacy in surgery

There is a significant effect of rFVIIa treatment in terms of reduction in the number of patients being exposed to allogeneic RBC transfusions, regardless of the dose applied (55.7% vs 67.6%)

In the subgroup analysis only patients receiving at least 50 µg/kg of rFVIIa, had a significant benefit (64.9% vs. 68.4%)

The cost benefit ratio is favorable only in patients who need a huge number of RBC units (> 40)