Aprotinin in cardiothoracic surgery

Outline

- Dangerous misconceptions in current cardiac anesthesia practice
- Comparative efficacy of aprotinin and tranexamic acid
- Aprotinin:
  - Mechanisms of action
  - Indication(s)
  - Administration and dosage
  - Safety issues

Dangerous misconceptions in cardiac anesthesia / surgery

1. Due to the advances in surgical techniques / CPB management / anesthesia management, bleeding is no longer a major issue in cardiac surgery.

2. Due to patient blood management concepts, we are administering much less blood transfusions.

3. Blood transfusions have become remarkably safe.

4. Tranexamic acid is an effective and safe drug that has helped to reduce blood transfusions in cardiac surgery dramatically.

Conflicts of interest – financial disclosures

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<thead>
<tr>
<th>Company</th>
<th>Nature of Affiliation</th>
<th>Unlabeled Product Usage</th>
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<tbody>
<tr>
<td>Nordic Pharma</td>
<td>Speaker's fees</td>
<td>None</td>
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Aprotinin: Aprotinin in cardiothoracic surgery
CABG:

- Estimated blood loss 400 mL (± 200 mL) after standard CABG.
- Up to 1,200 mL blood loss in patients treated with aspirin and clopidogrel.
- Whether bleeding is reduced by off-pump techniques is controversial.
- 5 to 7% of patients lose >2 L of blood.
- Up to 5% of patients require re-intervention for bleeding after sternotomy closure.


Incidence of bleeding in cardiac surgery

Impact of bleeding in cardiac surgery

Clinical significance and determinants of the universal definition of perioperative bleeding classification in patients undergoing coronary artery bypass surgery


Incidence of transfusion in cardiac surgery

We are still transfusing the majority of patients........

Incidence of transfusion in cardiac surgery

... and we have not become better!
In cardiothoracic surgery, blood transfusion is generally considered safe... but not in cardiac surgery. Blood transfusion is NOT safe in cardiac surgery.


Aprotinin in cardiothoracic surgery

Blood transfusion is NOT safe in cardiac surgery.

Aprotinin in cardiothoracic surgery

We do have tranexamic acid – why then bothering about aprotinin?

Aprotinin in cardiothoracic surgery

RESULTS:
- CPB was used in 2342 patients; 98.9% received tranexamic acid.
- Major transfusion (defined as 4 or more red blood cell units) was required in 758 patients (23%).

We do have tranexamic acid – but it is less efficacious than aprotinin

Aprotinin:
- Decreased risk of being transfused
- Lower incidence of re-thoracotomy (2.45 vs. 6.1%, P < 0.01)
- Lower mortality in open heart procedures (7.55 vs. 16.2%, P = 0.02)

Mortality associated with administration of high-dose tranexamic acid and aprotinin in primary open-heart procedures: a retrospective analysis

Before withdrawal of aprotinin:
- Less bleeding
- Less transfusion requirements
- Less re-thoracotomy
- Shorter hospital LOS
- Lower mortality in high-risk patients
Aprotinin in cardiothoracic surgery

We do have tranexamic acid – but it is less efficacious than aprotinin

- Large multicentre observational study before / after
- 4 tertiary care teaching hospitals (Haut-Lévêque Hospital in Bordeaux, Pitié-Salpêtrière Hospital and Bichat-Claude Bernard Hospital in Paris, and Laennec Hospital in Nantes).

Aprotinin in cardiothoracic surgery

We do have tranexamic acid – but it is less safe than previously thought
We do have tranexamic acid – but it is less safe than previously thought

Differences between tranexamic acid and aprotinin

Aprotinin: Enzyme inhibition beyond the coagulation system

Practical recommendations
Indication for aprotinin

Therefore the CHMP concluded that the balance of risks and benefits for aprotinin is positive under normal conditions of use subject to the revision of the indication as follows:

"Prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery)."
Aprotinin in cardiothoracic surgery

Practical recommendations

Indication for aprotinin

High risk patients do have the greatest benefit! (and less harm?)

Practical recommendations

Administration & dosing

Aprotinin – Safety

Anticoagulation on CPB

- Aprotinin is not heparin sparing: Initial bolus of unfractionated heparin 300-400 IU/kg
- One of three methods is recommended to maintain adequate anticoagulation with heparin:
  - Activated Clotting Time (ACT)
  - Fixed heparin dosing
  - Heparin titration according to heparin levels
- Recommended ACT tests:
  - Heparin-ACT > 480 s
- Aprotinin prolongs all methods measuring aPTT → aPTT must not be used to guide coagulation therapy up to 6-12 hours after stop of aprotinin (t1/2 ≈ 150 min)
- Neutralization of heparin with protamine (1 mg / 100 IU heparin)
- Aprotinin has a dose-dependent inhibitory effect on the action of thrombolytic agents, e.g. streptokinase, urokinase, alteplase (r-tPA)
Aprotinin – Safety

Renal function

- Consistent signal from clinical trials: aprotinin therapy is associated with statistically significant rises in plasma creatinine (overloading of tubular reuptake mechanisms by aprotinin)
- No evidence that aprotinin therapy is associated with an increased risk of renal failure or need for RRT
- Careful consideration of the risk-benefit ratio in patients with pre-existing impaired renal function or those with risk factors (such as concomitant treatment with aminoglycosides or contrast agents)
- Dosing scheme has not to be adjusted in patients with severely impaired renal function (although elimination half-life is prolonged)
- Loss of aprotinin (6,500D) during hemofiltration on CPB (cut-off 14,000D)

Hypersensitivity – Anaphylactic reaction

- Risk of hypersensitivity reactions = primarily related to exposure history.
  - Incidence (%)
  - Re-exposure within 6 months: 5
  - Re-exposure after 6 months: 0.9
  - No prior exposure: 0.1
- “An appropriate aprotinin-specific IgG antibody test may be considered before administration of aprotinin” (commercially not available)
- No re-exposure within 12 months
- TEST DOSE: 1ml (10,000 KIU) at least 10 min prior to the loading dose.
  - H1 / H2 antagonist may be administered 15 min prior to the test dose.
  - Slow injection!
  - Caution: Fibrin glue!

SUMMARY

- Despite all advances, bleeding remains a major issue in cardiac surgery
- Both bleeding and transfusion lead to an excess in morbidity and mortality
- TXA is in widespread use – but less effective than aprotinin
- Aprotinin demonstrates clinical efficacy & safety in reducing
  - Bleeding, transfusion, re-exploration for bleeding
  - Morbidity and mortality
- Aprotinin is more than an antifibrinolytic
- Aprotinin is currently approved only for CABG on CPB in patients with major bleeding risk

Thank you very much for your attention
Blood transfusion is safe...

Practical recommendations
Indication for aprotinin

Identification of the patient at “high risk for major blood loss”

Practical recommendations
Administration scheme

<table>
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<tr>
<th>DOSEAGE</th>
<th>ADMINISTRATION</th>
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<tr>
<td>Test dose</td>
<td>10,000 KIU (1 ml)</td>
</tr>
<tr>
<td>Loading dose</td>
<td>1-2 million KIU (2-4 ml of 500 KIU/ml)</td>
</tr>
<tr>
<td>Continuous infusion during surgery</td>
<td>250,000-300,000 IU per hour (0.5-1 ml per hour)</td>
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<tr>
<td>&quot;Pump prime&quot; dose</td>
<td>1-2 million KIU (2-4 ml of 500 KIU/ml)</td>
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To avoid physical incompatibility of aprotinin and heparin when adding to the pump prime solution, each agent must be added during reconditioning of the pump prime to sterile physiological solution prior to administration with the other component.