Alternatives to transfusion: caveats

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Demands for medical alternatives to blood transfusion

- Jehovah’s Witnesses
- Surgeons
- Anesthetists
- Hematologists
- Hospital managers
- Network for Advancement of Transfusion Alternatives (NATA)
Reasons for demand for medical alternatives to blood transfusion

- Risks on transfusion transmittable infections
- Risks on higher incidence of infections
- Risks on immune modulation
- Risks on decreased patient survival
- Safety of blood transfusion
- Questions on the efficacy of blood transfusion
- Lack of sufficient supply
- Costs
Costs

In the Netherlands, the incremental cost-effectiveness ratio of

- Triplex NAT (HBV, HCV, HIV), in addition to serologic testing: € 5.20 million per quality-adjusted life-years (QALY)

- Anti-HTLV-I/II: € 45.2 million / QALY

- HAV NAT: € 18.6 million / QALY

Medical alternatives to blood transfusion

Surgical devices to minimize blood loss
- laser surgery
- electrocautery
- electrosurgery, etc.

Techniques and devices to control bleeding and shock
- controlled hypotension
- shock position
- prompt surgery
- ice packs, etc.

Surgical and anesthetic techniques to limit blood loss
- hypotensive anesthesia
- induced hypotermia
- acute normovolemic hemodilution
- hypervolemic hemodilution
- intraoperative / postoperative blood salvage
- arterial embolization, etc.

Devices and techniques that limit iatrogenic blood loss
- essential tests only
- microsampling, etc.
Medicinal alternatives to blood transfusion

Volume expanders

* **Crystalloids**
  - Ringer’s lactate
  - Normal saline
  - Hypertonic saline

* **Colloids**
  - Pentastarch/ Hetastarch
  - Gelatin
  - Dextran

Hemostatic agents for bleeding / clotting

- Aprotinin
- Conjugated estrogens
- Vasopressin
- Recombinant factor VIIa

Therapeutic agents for managing anemia

- Hemoglobin solutions
- Perfluorocarbon-based oxygen carriers
- Hematinics (iron, folic acid, vitamin B12)
- Erythrocytes stimulating agents (ESAs)
What about … ?

- Risks
- Safety
- Efficacy
- Supply
- Costs
Examples

- Hemoglobin-based oxygen carriers
- Erythrocytes stimulating agents (ESAs)
- Plasma substitutes for albumin
Therapeutic agents for managing anemia

- Hemoglobin solutions
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- Hematinics (iron, folic acid, vitamin B12)
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Hemoglobin-based oxygen carriers

- Surface-modified haemoglobin
- Intramolecular cross-linked haemoglobin
- Liposome-encapsulated haemoglobin

- Indications:
  - situations where red cells are unavailable: military actions
  - universal compatibility with all blood types
  - freedom from transmission of TTI
  - prolonged storage under extreme circumstances
Haemoglobin solutions
Biopure
Northfields
Sangart

Perfluorocarbons
Alliance
Oxycyte
Perftoran

Cultured red cells
Biopure

- Medicine from food grade cows ???
- Claim complete prion removal
- Licensed in South Africa
- Licensed as a veterinary medicine.
- Used in 1000 + patients in elective surgery
- Further clinical trials in US suspended;
- Under investigation by SEC
Hemoglobin-based oxygen carriers

Adverse events:

- All: vasoconstriction, reduction of cardiac output, jaundice, myocardial infarction, stroke, acute renal insufficiency, increased arterial blood pressure, methemoglobinemia, increased liver enzymes, and deaths. Gastrointestinal discomfort can occur.
- Diaspirin cross-linked hemoglobin: increased mortality
- O-raffinose cross-linked hemoglobin: cardiac problems

Perfluoro-carbons

100 mls = 1 to 4 units of red cells

Can be used to very low haematocrits
Phase III study terminated due to possible increase of strokes
• Produced and licensed in Russia since 1997

• January, 21, 2005: Lectures on clinical application of Perftoran in infusion-transfusion therapy in the Centre of Science of Surgery of Russian Academy of Medical Science, Moscow

• Main adverse events: hypotension; pulmonary complications (1% in randomized trial); allergic reactions in particular after inappropriate warming

E. Zhiburt, personal communication

Cohn CS, Cushing MM Crit care Clin 2009;25(2):399-414
Perfluorocarbons

- Adverse events:
  - complement activation
  - reduced platelet function

- Perfluoro-octyl bromide:
  - clinical trial has stopped: increased incidence of stroke in cardiac by-pass patients

- New perfluorocarbon emulsion:
  - increased blood viscosity

Erythrocytes stimulating agents (ESAs)

- Recombinant human erythropoietin (rHuEPO)
  - Epoetin alfa (t½: 8 hrs)
  - Epoetin beta (t½: 8 hrs)
- Darbepoetin alfa (t½: 49 hrs)
Erythrocytes stimulating agents (ESAs)

Indications:
- Correction of anemia in chronic renal disease
- Correction of anemia related to cancer or cytotoxic drugs
- Chronic heart failure
- Acute myocardial infraction
- Anemia after cardiac transplantation

Experimental:
- Stroke; diabetes; reduction of red cell transfusions; critically ill patients

Not approved:
- Symptoms of anemia (in surgical patients; patients with HIV infection; fatigue in patients with cancer)
Adverse events of ESAs

• Common: Injection site reactions; purities; influenza-like symptoms; peripheral edema; non-specific rashes; dyspnoe; upper respiratory infections; hypertension; seizures; procedural hypertension; nasopharyngitis; muscle spasms; pyrexia; hypokalemia; hypophosatamia.

• Increased risk: Cardiovascular/ thromboembolic events (partly due to effects of increased Hb on viscosity / platelet-erythrocytes interactions or direct effects of erythropoietin on platelets or vascular endothelial cells); pure red cells aplasia.

Safety of EPO

Analysis of 12 randomized controlled trials
- rHuEPO vs placebo
- Anemic patients with cancer
- 1.55 times increased risk on thromboembolic events
- 1.25 times increased risk on hypertension


Updated review of 57 trials and 9,35 patients with cancer
- Significant reduction of red cell transfusions
- Increased risk on thromboembolic events

Safety of EPO

• In 5-10% of patients: hypo-responsiveness

• Prospective randomized placebo-controlled trial:
  - n = 1460 surgical or trauma patients
  - dose EPO 40,000 U or placebo
  - weekly for max. 3 weeks
  - follow up 140 days

No reduction of incidence of red cell transfusions
Thrombotic vascular events: 16.5% vs 11.5%
Thrombotic vascular events in pts without heparin: 20.3% vs 12.8%
Thrombotic vascular events in pts with 3 doses EPO: 22.8% vs 16.1%

Safety of EPO

Concerns:
- Neurovascular diseases: risk on cerebral ischemia due to increased blood viscosity
- Potential progression of cancer due to blocking of tumor cell apoptosis, stimulating chemotaxis, increased metastatic disease, assisting in tumor genesis

- Meta-analysis (12 randomized controlled studies in 2297 patients)
  Epoetin-beta: no detrimental effect on survival or tumor progression when given at Hb concentrations of up to 11 g/dl. Unfortunately, the Hb response to epoetin-alfa is unpredictable.

In cancer-induced anemia, ESAs should be given at the lowest possible dose to prevent the need for erythrocyte transfusions.

Safety of EPO

FDA Public Health Advisory, 2007

- Based 4 studies in cancer patients
- Unapproved dosage regimen and unapproved patient population
  - Higher incidence of death
  - Increased rate of tumor growth; when EPO was given to maintain Hb-level > 12g/dl
  - Higher chance of death without reduction of blood use when EPO was given in cancer patients with anemia not receiving chemotherapy
  - Higher chance of blood clots in patients scheduled for major surgery
Plasma substitutes for albumin

- Hydroxy ethyl starches
- Dextran
- Gelatins

All increased risks on:
- anaphylactic reactions:
  - hydroxyl ethyl starch: 4.51 per 10^5 infusions
  - dextran: 2.32 per 10^5 infusions
  - gelatine: 12.4 per 10^5 infusions


- renal impairment

Davidson Eur J Anaesthesiol 2006;23(9):721-38
Plasma substitutes for albumin

- Dextran - The incidence of acute renal insufficiency associated with dextran is estimated to be 4.3% in dehydrated patients.


- Hydroxyethyl starch (HES) is strongly associated with acute kidney damage and a need for renal replacement therapy.

Update on the Comparative Safety of Colloids: a systematic review of clinical studies – discussion

- Papers of Prof. Joachim Boldt (102 from 1999 onwards)
- 88 papers lacked approval of Ethics Committee → retraction
- Boldt strongly advocated the use of HES in place of albumin

- 2 in this review were positive for albumin
  - 5 others in this review compared different colloids
  - Prof. Joachim Boldt has been dismissed from his post as head of anesthesiology at the Klinikum Ludwigshafen in Germany, after an investigation uncovered multiple fraudulent activities relating to a clinical study published last year comparing the use of HES to 5% human albumin for cardiopulmonary bypass pump priming (HES better than albumin)
  - No Institutional Review Board approval
  - No written informed consent
  - No randomization process
  - No follow-up questionnaire


Groeneveld et al, Ann Surg 2011 Jan 6
Summary

EMA guidelines on adverse events (AE) rates:

• Common: > 1 AE per 100 administrations
• Uncommon: < 1 AE per 100 but > 1 AE per 1000 administrations
• Rare: < 1 AE per 1,000 but > 1 per 10,000 administrations
• Very rare: < 1 AE per 10,000 administrations

Haemovigilance schemes:

Data of Ireland and Greece

Hemolysis due to ABO incompatibility: 1 per 187,845 units
TACO: 1 per 10,436 units
Possible transfusion transmitted bacterial infection: 1 per 187,845 units
Anaphylaxis / hypersensitivity: 1 per 4,696 units
Incidence of SAEs: 0.9 per 10,000 whole blood units
0.65 per 10,000 blood products
Incidence of non-SAEs: 12 per 10,000 whole blood units
8.3 per 10,000 blood products
Summary

Medicinal alternatives to blood are:

• not that harmless
• even unsafe, at least some products, as considered by authorities,
• facing higher adverse events rate compared to blood components
- Whether alternatives to blood have a safety profile superior to blood should be reconsidered carefully

- Efforts should be made on data collection on (serious) adverse events rates of medical alternatives to blood

- Erythropoetin is administered unnecessarily and is more expensive than red cell transfusions. 
  

- Blood transfusion committees should be informed on pro’s and con’s of blood alternatives

- Haemovigilance systems should consider whether alternatives to blood should be included in their objectives
Questions?

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