ERYTHROPOIETIC STIMULATING AGENTS IN THE ICU: A MOVING PUZZLE

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FACULTY DISCUSSANT
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OCT. 24, 2014
CASE PRESENTATION

- 25 F, a Jehovah’s witness, w/ h/o synovial sarcoma in left thigh s/p surgical tx who was readmitted for residual disease resection
- Underwent left thigh sarcoma removal w/ femoral vein ligation and femoral artery resection and reanastomosis
- EBL was 600 ml, and Heparin gtt started for thrombosis pp
- She had normal pre-operative HCT at 42, and post-operative HCT 34
- Four days after surgery, US revealed 13 cm hematoma in left thigh
- Developed severe headache, vertigo and soft BP w/ HCT 14
- She was transferred to ICU and hematology was consulted
MANAGEMENT OF JW PTS W/ BLEEDING

Legal issues
• Determine what products are acceptable (if any) / Determine POA

Control acute bleeding
• Embolization
• External radiation therapy
• Hormone therapy

Correct coagulopathy
• Reverse anti-coagulation therapy/Vitamin K
• Cryoprecipitate (if allowed)
• Avoid anticoagulation/antiplatelet agents

Maximum oxygen delivery/decrease oxygen demands
• Oxygen support to increase oxygen delivery

Limited blood drawn
• Pediatric tube or even finger stick

Stimulate erythropoiesis
• Erythropoietin stimulating agents
• Vitamin B12
• Folic acid
• Iron

UWMC/FHCRC/SCCA:
► Specific consent
► Acute normovolemic hemodilution
► Bloodless Surgery Guidelines

Am J Obstet Gynecol 2011;205(2).e5-8
Should erythropoietin be given in the ICU setting?

- Trials using ESAs in the ICU
- ESA dosing in the ICU
Erythropoiesis

EPO acts here

7 days to mature from a CFU-E to a reticulocyte

ESAs can stimulate growth or survival of other nonhematopoietic cell types, including tumor cells.

ANEMIA ETIOLOGY IN ICU

Trauma
(accident, operation, myocardial infarct, stroke)

- Hemorrhage
- Hemolysis

Phlebotomy

Immune reaction
- IL-1, TNF-α ↑
- IL-6 ↑

Epo ↓

Hepcidin ↑

Inhibition of erythropoiesis

Iron availability ↓

Anemia

MORE PRBC TRANSFUSED IN ICU

- 95% of ICU pts develop anemia in ~3 days
- 42-50% of pts in ICU require PRBC transfusion
- PRBC requirement is a/w the length of ICU stay
  70% of pts require PRBC if ICU stay ≥ 7 days
  85% of pts require PRBC transfusion if stay ≥ 13 days
- Annually, nearly 15 million units of PRBCs were transfused in US, but the physiologic basis for transfusion in the ICU is controversy

*JAMA. 2002;288:1499–1507.*
RISKS of PRBC TRANSFUSIONS

1 in 100 million
1 in 10 million
1 in 1 million
1 in 100,000
1 in 10,000
1 in 1,000
1 in 100
1 in 10
1 in 1

HIV
HCV
HBV
TRALI
Life-threatening reaction
Fatal hemolysis

TACO
Fever

Motor vehicle fatalities
Firearm homicide
Airplane fatalities
Death from medical error
Fall fatalities
Lightning fatalities

RISK

POSSIBLE BENEFITS OF ESAs

- RBC production has decreased in ICU pts and their Epo production is inappropriately low

- Avoid transfusion adverse effects

- Augment the delivery of $O_2$ to avoid deleterious effects of $O_2$ debt

- Improve tissue healing
**EPO-1: ESAs REDUCE PRBC TRANS.**

<table>
<thead>
<tr>
<th>Transfused PRBCs</th>
<th>GROUP (N=160)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rHuEPO (N=80)</td>
<td>Placebo (N=80)</td>
<td></td>
</tr>
<tr>
<td>Total units transfused</td>
<td>166</td>
<td>305</td>
<td></td>
</tr>
<tr>
<td>%Transfused days 8-42</td>
<td>45</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>HCT change (baseline to final)</td>
<td>4.8 (95% CI 3.8-5.9)</td>
<td>1.4 (95% CI 0.3-2.8)</td>
<td></td>
</tr>
<tr>
<td>Final HCT</td>
<td>35.1 ± 5.6</td>
<td>31.6 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte % change</td>
<td>2.5 (95% CI 1.9-3.0)</td>
<td>0.8 (95% CI 0.3-1.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Event Frequency (no difference)**

<table>
<thead>
<tr>
<th>Event</th>
<th>rHuEPO (N=80)</th>
<th>Placebo (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Dose: 300 IU/kg, started day 3 and continuously daily for total of 5 days. Then every other day.
Criteria: HCT < 38%

PRBC TRANS. THRESHOLD IN ICU

TRICC in 1999

• 838 pts studied: 418 pts w/ Hgb at 7.0-9.0 g/dl (restrictive), and 420 pts w/ Hgb at 10.0-12.0 g/dl (liberal)
• 30-day mortality was similar.
• The mortality rates were lower w/ the restrictive transfusion in pts less acutely ill and in pts who < 55

RBC transfusion guideline by AABB based on systematic review of RCTs from 1950-2011:

• A restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable pts
• Use restrictive strategy in hospitalized pts with preexisting CV disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less

**EPO-2: WEEKLY ESAs REDUCE PRBC TRANS.**

- Dose regimen: rHuEPO 40,000 IU started at day 3 weekly
- Transfusion criteria: maintain Hgb > 8.5 g/dl, comparable to the transfusion practice pattern observed in the TRICC trial.

<table>
<thead>
<tr>
<th>PRBC Transfused</th>
<th>rHuEPO (N=650)</th>
<th>Placebo (N=652)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units transfused per pts Mean (SD)</td>
<td>2.4 (4.79)</td>
<td>3.0 (5.42)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total No. of days alive</td>
<td>16247</td>
<td>16235</td>
<td></td>
</tr>
<tr>
<td>Total No. of units transfused</td>
<td>1590</td>
<td>1963</td>
<td></td>
</tr>
<tr>
<td>Transfusion rate/days alive (SE)</td>
<td>0.098 (0.0074)</td>
<td>0.121 (0.0085)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Adverse Event**

| Any serious events   | 235        | 249        | 0.45     |

*JAMA 2002; 288(22):2827-2835.*
**EPO-3: SURVIVAL BENEFIT**

- Dose regimen: rHuEPO 40,000 IU started at day 3, weekly
- Transfusion criteria: maintain Hgb > 8.0 g/dl
- Hgb at day 29: 1.6±2.0 g/dl in the rHuEPO group vs. 1.2±1.8 g/dl in the placebo group, \( P < 0.001 \).
- Did not reduce the PRBC transfusion, unexpected finding

<table>
<thead>
<tr>
<th>Group</th>
<th>rHuEPO</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 29</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>63/733</td>
<td>83/727</td>
<td>0.79 (0.56-1.10)</td>
</tr>
<tr>
<td>Trauma</td>
<td>14/402</td>
<td>26/391</td>
<td><strong>0.37 (0.19-0.72)</strong></td>
</tr>
<tr>
<td><strong>Day 140</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>104/733</td>
<td>122/727</td>
<td>0.86 (0.65-1.13)</td>
</tr>
<tr>
<td>Trauma</td>
<td>24/402</td>
<td>36/391</td>
<td><strong>0.40 (0.23-0.69)</strong></td>
</tr>
</tbody>
</table>

*NEJM 2007;357(10):965-976.*
ESAs REDUCE TRAUMA PTS MORTALITY

Observed 29-day mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>rhEpo</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO-2</td>
<td>4.1%</td>
<td>8.9%</td>
<td>0.43 (0.23-0.81)</td>
</tr>
<tr>
<td>EPO-3</td>
<td>3.5%</td>
<td>6.6%</td>
<td>0.37 (0.19-0.72)</td>
</tr>
<tr>
<td>Trial-4†</td>
<td>7.9%</td>
<td>24.2%</td>
<td>0.27 (0.12-0.62)</td>
</tr>
</tbody>
</table>

EPO trials

- VTEs increased if not on heparin ppx

† Prospective observational study in traumatic brain injury pts

- Data represent in-hospital mortality
- Longer lengths of ICU stay
- Cost-effective unclear

ESAs IN MYOCARDIAL DISEASE: CONFLICTING

<table>
<thead>
<tr>
<th>Study</th>
<th>Case (N)</th>
<th>↑ LVEF</th>
<th>↓ Stent thrombosis</th>
<th>↓ Infarct size</th>
<th>↓ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVEAL</td>
<td>STEMI</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(222)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-1</td>
<td>STEMI</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(1244)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-2</td>
<td>AMI</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(1564)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REVEAL trial
- 222 pts with STEMI and PCI
- End point as death, MI, stroke or stent thrombosis
- Mortality: 5/125 in rhEpo vs 0/97 in placebo

JAMA. 2011; 305(18):1863-72.
ESAs: NO NEUROPRECTION IN STROKE

• Severe anemia could be harmful in brain-injured pts, stimulate erythropoiesis may benefit nerve recovery
• ESAs could be applied for neuroprotection since Epo was assigned pleiotropic anti-apoptotic potential

German Multicenter EPO Stroke Trial
• The use of rhEpo for neuroprotection resulted in a higher death rate, particularly in pts requiring thrombolytic therapy.
• In anemic stroke pts ESAs are of little help because of the delay in RBC production.
• In non-anemic stroke pts ESAs may be harmful d/t AEs resulting from the stimulation of erythropoiesis, particularly the risk to promote thromboembolism

DO ESAs IMPROVE BURN INJURY?

- Propective double-blinded randomized trial of 40 pts
- rhEpo use in the acutely burned pts did neither prevent the development of postburn anemia nor decrease transfusion requirements.

- Retrospective of rhEpo use in 25 pts
- No effect on mortality or RBC transfusion requirements in the severely burned

- A prospective, randomized, double-blind, multicenter study
- Investigate the effects of rhEpo treatment in severely burned pts
- Anemia is not the primary treatment goal
ESAs FOR TISSUE PROTECTION?

- Preclinical observations: Epo is a pleiotropic survival factor with ubiquitous anti-apoptotic properties

*Do ESAs protect tissues in ICU pts?*

- Solely hematopoietic tissues have high levels of Epo receptor molecules with undetectable levels in non-hematopoietic tissues

![Diagram showing fluorescence intensity of EPOR, GATA-1, and SCL/TAL1 in different tissues.
CD105+ endothelial
CD71+ early erythroid]
HIGH DOSE ESAs REQUIRED IN ICU

- The dose of rHuEPO:
  2,000–8,000 IU/wk in anemic CKD pts
  30,000–40,000 IU/wk rhEpo in cancer pts on chemotherapy
- What is the appropriate dose for pts in ICU?
  ESA resistance: inflammatory mediators impair iron availability and erythropoietic cell proliferation
- Epo-induced increases in Hb develop very slowly in critically ill pts due to the inflammatory processes
- There was little further improvement in patients receiving SC 40,000 IU rhEpo three times a week
- Six doses used
  40,000 IU/wk SC (group A) or IV (group B)
  15,000 IU qod SC (group C) or IV (group D)
  40,000 IU day 1 and 3, SC (group E) or IV (group F) followed by 15,000 IU qod on days 5-15
- all dosing regimens were well tolerated and appeared to affect reticulocytosis, with a peak at day 11 or 15

CONCLUSIONS

• At present, the use of ESAs in ICU is off-label, unless the pt has an approved clinical indications.

• In some distinct situations, ESAs may be considered an exceptional therapy. Those include:
  ■ *Trauma, particularly with traumatic brain injury*
  ■ *Jehovah's Witnesses who refuse allogeneic blood transfusions due to religious beliefs*

• The use of ESAs increase Hgb concentration and had potential effect on overall mortality, although it may not reduce PRBC transfusion in ICU pts.

• Due to ESA resistance, high dose ESAs is required in ICU.