Extra-corporeal Techniques to Remove Humoral Factors in Sepsis

The evidence

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Published literature

- Haemofiltration
- Plasmafiltration
  - In sepsis / SIRS

- Excluded:
  - not sepsis, subgroup analysis unclear
Principles

• Systemic Inflammatory Response Syndrome
  – Toxins
  – Inflammatory response
• Remove the “evil humors”
  – Bacterial toxins
    • Lipo-polysaccharide endotoxin
    • Exotoxins
  – Pro-inflammatory cytokines
    • e.g. TNFα, IL1/2/8, PAF, C3a/5a, etc
• +/- replace consumed factors
  • e.g. IL6/10, Ig, protein C
Variables

Fluids
- Crystalloid
- Albumin
- Plasma

Access
- Arterio – venous
- Veno – venous

Infective agent
- route

Animal

Duration

Flow rates
- Filtration rate
- Blood flow

Additional techniques
- Dialysis
- Adsorption

Outcome measures
- Survival
- Clinical
- Immunological
Haemofiltration animals

Sheep, 1
Dogs, 4
Rats, 1
Pigs, 7
Haemofiltration animals

- **Infective agent**
  - Endotoxin
  - Bacterial culture (*E. coli*, *S. aureus*, *P. aeruginosa*)
  - IV, intraperitoneal clot, inhalation
  - Sup. Mesenteric Art / caecal ligation

- **Access:**
  - CAVH 8; CVVH 5

- **Start time:** before BP vs after
## Haemofiltration dogs

<table>
<thead>
<tr>
<th>Filtration ml/kg/hr</th>
<th>Duration hours</th>
<th>Mortality treatment</th>
<th>Mortality control</th>
<th>Other effects of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>3</td>
<td>0/12</td>
<td>0/26</td>
<td>Improved haemodynamics</td>
</tr>
<tr>
<td>50-80</td>
<td>2-3</td>
<td>0/8</td>
<td>0/14</td>
<td>Improved LV contractility</td>
</tr>
<tr>
<td>80</td>
<td>3</td>
<td>0/8</td>
<td>0/8</td>
<td>Higher mean blood pressure</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>6/7</td>
<td>11/14</td>
<td>None</td>
</tr>
<tr>
<td>Filtration (ml/kg/hr)</td>
<td>Duration (hours)</td>
<td>Mortality treatment</td>
<td>Mortality control</td>
<td>Other effects of treatment</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>160</td>
<td>3.5</td>
<td>0/6</td>
<td>1/12</td>
<td>Improved haemodynamics</td>
</tr>
<tr>
<td>167</td>
<td>2.5</td>
<td>2/6</td>
<td>6/6</td>
<td>Improved haemodynamics</td>
</tr>
<tr>
<td>1.2-2.5</td>
<td>6</td>
<td>20/20</td>
<td>20/20</td>
<td>Longer survival</td>
</tr>
<tr>
<td>100-200</td>
<td>6</td>
<td>6/7</td>
<td>7/7</td>
<td>Longer survival with larger pore</td>
</tr>
<tr>
<td>20</td>
<td>4.5</td>
<td>4/10</td>
<td>7/10</td>
<td>Lung mechanics better</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>0/8</td>
<td>0/8</td>
<td>No clinical difference</td>
</tr>
<tr>
<td>25</td>
<td>24</td>
<td>0/7</td>
<td>0/14</td>
<td>None</td>
</tr>
</tbody>
</table>
### Sheep

<table>
<thead>
<tr>
<th>(Rogiers 2006)</th>
<th>Blood warmed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>90</td>
<td>38</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Mortality &lt;16h</td>
<td>0/10</td>
<td>10/10</td>
</tr>
</tbody>
</table>

Metabolic acidosis & Lactate less in warmed
Immunological

- TNF & PGF1
  - ? (Bellomo 2000)
  - Not significantly different (Ishihara 1999)
- Pore size (Lee 1998)
  - 50 KD survival 56 hrs
  - 100 KD survival 103 hrs
- Ultrafiltrate (Grootendorst 1992)
  - Causes death on infusion to non-septic pigs
Study methods

• **Control** (Freeman 1995)
  – Not filtered (mortality 14%)
  – Filtered (mortality 29%)
  – +/- ultrafiltrate re-infused (Lee 1993)

• **Outcome**
  – 2 studies numbers too small for statistical significance
  – 8 benefit
  – 3 no benefit
<table>
<thead>
<tr>
<th>Blood flow ml/min</th>
<th>Duration hours</th>
<th>Mortality</th>
<th>Effect of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>-</td>
<td>0/1</td>
<td>Improved haemodynamic</td>
</tr>
<tr>
<td>450</td>
<td>4</td>
<td>11/20</td>
<td>Improved haemodynamic</td>
</tr>
<tr>
<td>300</td>
<td>4</td>
<td>2/24</td>
<td>Improved haemodynamic</td>
</tr>
<tr>
<td>-</td>
<td>36</td>
<td>1/1</td>
<td>Coagulopathy improved</td>
</tr>
<tr>
<td>400-750</td>
<td>-</td>
<td>7/9</td>
<td>None</td>
</tr>
<tr>
<td>2-145</td>
<td>26</td>
<td>14/19</td>
<td>None</td>
</tr>
</tbody>
</table>
Case studies

• Conditions
  – Sepsis +/- ARDS (Gotloib 1986)
    ARF (Tonnesen 1993)

• Outcomes
  – Cardiac index – improved 50%
  – SvO₂ – increased 25%
  – Inotropes – decreased requirement
    • Others no significant metabolic, resp, haem change

• Bias in reporting +ve outcomes
Human haemofiltration trials

• 9 prospective studies
  – 5 non-randomised cohort:
    • $n = 5$ (Hoffmann 1999) $10$ (Kodama 1997)
    • $16$ (Hoffmann 1995) $18$ (Heering 1997)
    • $18$ (Bellomo 1995)

• Conditions:
  – Sepsis (6), SIRS (3) +/-
    • MOF (Bellomo 1995)
    • ARF (Bellomo 1993; Heering 1997; Kellum 1998)

• Filtration rates
  – 0.4 – 2 L/hr (6 - 30 ml/kg/hr)
Controlled haemofiltration trials

• Outcome:
  – 4 cytokine levels (no clinical differences)
    • TNF & IL-1 in ultrafiltrate but levels unchanged (none in controls)
  – 2 effect of ultrafiltrate
    • ?myocyte contractility
    • Monocyte ?TNF, ?IL-2 & IL-6

• Cohort mortality rates
  – 7/10 (Kodama 1997)
  – 12/18 (Heering 1997) Non-significant ? mortality
## RCT haemofiltration trials

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Flow ml/min</th>
<th>Duration hrs</th>
<th>Mortality</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>150</td>
<td>48</td>
<td>9/13</td>
<td>Non-significant ? mortality</td>
</tr>
<tr>
<td>RCT</td>
<td>100-120</td>
<td>48</td>
<td>5/15</td>
<td>Non-significant ? mortality</td>
</tr>
<tr>
<td>RCT (adsorption)</td>
<td>-</td>
<td>2</td>
<td>17/37</td>
<td>Non-significant ? mortality</td>
</tr>
<tr>
<td>RCT (crossover)</td>
<td>-</td>
<td>24</td>
<td>12/13</td>
<td>None</td>
</tr>
</tbody>
</table>
molecular adsorbents recirculating system (MARS)

CVVH
Plasmapheresis animal studies

- **Animals**
  - **Rats** (Cohen 1987)
    - Can tolerate endotoxin > humans
  - **Rabbits** (Tetta 2000)
    - 109 rabbits in 9 arms
    - Similar sensitivity to LPS of *E. coli* as humans

- **Toxin**
  - Endotoxin (3), *E. coli* (IP Natanson 1993; IV Busund 1991)

- **Adsorption**
  - Polymyxin B (binds endotoxin) (Cohen 1987)
  - Reverse phase resin (Tetta 2000)
<table>
<thead>
<tr>
<th>Animal</th>
<th>Method</th>
<th>Blood flow ml/min</th>
<th>Duration hours</th>
<th>Mortality treatment</th>
<th>Mortality control</th>
<th>Other effects of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>PF &amp; adsorptn</td>
<td>-</td>
<td>1.5</td>
<td>0/4</td>
<td>4/4</td>
<td>Haematological improved</td>
</tr>
<tr>
<td>Rabbit</td>
<td>PF &amp; adsorptn</td>
<td>10</td>
<td>3</td>
<td>3/19</td>
<td>30/40</td>
<td>No difference haemodynamic</td>
</tr>
<tr>
<td>Dogs</td>
<td>PF</td>
<td>20</td>
<td>1.5</td>
<td>0/6</td>
<td>7/8</td>
<td>Haemodynamic improved</td>
</tr>
<tr>
<td>Dogs</td>
<td>PF</td>
<td>100</td>
<td>2</td>
<td>6/6</td>
<td>5/6</td>
<td>Haemodynamic worse</td>
</tr>
<tr>
<td>Pigs</td>
<td>PF</td>
<td>30</td>
<td>1.25</td>
<td>-</td>
<td>-</td>
<td>Haemodynamic improved</td>
</tr>
</tbody>
</table>
Plasmapheresis case reports (n=9)

• Condition
  – 6 Meningococcal
  – 2 Pneumococcal
  – 2 Sepsis including feb neut, VZV, HUS
• 3 single cases & 3 series of 3 cases
  – all survived
• 1 blood exchange (survived) (van Deuren 1992)
• Mortality: 2/6, 1/8, 6/9, 8/12, 0/3
• Haemodynamic
  – 1: Improvement SVRI, CI, LVEJ, DO₂ (Berlot 1997)
  – 1: No difference VI, A-a DO₂, inotropes (Reeves 1995)
### Plasmapheresis and plasma exchange cohort studies

<table>
<thead>
<tr>
<th>Technique</th>
<th>Condition treated</th>
<th>Mortality treatment</th>
<th>Mortality control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma exchange</td>
<td>Meningococcaemia</td>
<td>1/13</td>
<td>6/10</td>
<td>P=0.025</td>
</tr>
<tr>
<td>Leuka-plasmapheresis</td>
<td>Meningococcaemia</td>
<td>3/13</td>
<td>7/9</td>
<td>P=0.02</td>
</tr>
<tr>
<td>Plasma exchange &amp; CVVHF</td>
<td>Septic shock</td>
<td>1/7</td>
<td>8/21</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Surgical sepsis</td>
<td>11/19</td>
<td>13/24</td>
<td>P=0.94</td>
</tr>
</tbody>
</table>
Plasmapheresis and plasma exchange RCT

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Control</th>
<th>Plasmapheresis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reeves 1999</td>
<td>6/14</td>
<td>8/16</td>
<td>0.73</td>
</tr>
<tr>
<td>– No difference survival or number organs failing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busund 2002</td>
<td>18/52</td>
<td>28/52</td>
<td>0.05</td>
</tr>
<tr>
<td>– 28d relative risk mortality 0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Number needed to treat 4.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CVVH +/- ECMO children

- PCCM 29 May 2007 Publish Ahead of Print
  Shaheen et al Nottingham, Sheffield, Leicester
CVVH +/- ECMO children

- Bacterial sepsis
  - 30 CVVH
  - 6 CVVH + ECMO
- Viral sepsis
  - 2 CVVH
  - 14 CVVH + ECMO
- All sepsis with MOF
  - 22/56 (39%) survived
- 4 meningococcal plasmaphiltration
  - 2 survived
Case example

22.2.06 1y/o?

- 150 ml/kg before admission
- Adrenaline 1.6 mcg/kg/min
- Noradrenaline 1 mcg/kg/min
- Milrinone 750 ng/kg/min
- Vasopressin
- pH 6.97, BE -20

- Anuric after 6hrs

CVVH

- Blood flow
  - 70 ml/min
- Replacement
  - 300 ml/hr
  - (30 ml/kg/hr)
- Balance
  - neutral
Summary – The evidence

• Haemofiltration
  – Animals: 8 benefit vs 3 no benefit
  – Human: 3 case studies improved haemodynamics
    12 studies (inc 3 RCT) no ? mortality

• Plasmafiltration
  – Animals: 3 improved, 1 worse
  – Human: retrospective – mortality lower 2; same 2
    prospective – mortality lower 1; same 1