Perioperative Corticosteroid Levels and the Adrenal Response Following Infant CPB

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2013 AATS Annual Meeting
Mayo Clinic
No disclosures
Cardiopulmonary Bypass (CPB) and Children

- Induces a systemic inflammatory response
  - Complement activation
  - Cytokine release
  - Cortisol levels increase

- Clinical manifestations
  - Low cardiac output
  - Hemodynamic lability
  - Fluid retention
  - Fever

Kozik Ann Thorac Surg 2006
Madhok Pediatr Cardio 2006
Bronicki Crit Care Med 2003
Potential Solution

Glucocorticoids
Consequences of Corticosteroids

- **Immunosuppression:**
  - Lymphocyte
  - T helper cell
  - Cytotoxic T cell
- **Neutrophil induction**
- **Cortisol suppression**
- **Glucose induction**
Clinical Consequences

- Pediatric Health Information System Database
- 46,730 children (0-18 yrs) undergoing CPB
  - 54% received corticosteroids
- Corticosteroid treated children had increased:
  - Infection rates
  - Insulin requirement
  - ICU and hospital length of stay

- Potential causes:
  - Over suppression of inflammatory/stress response

S Pasquali Circulation 2010; 122:2123-2130
The “appropriate” infant stress response??

- Unknown
- Wide range of post-op cortisol levels reported
- Variation in results are due to:
  - Study design
  - Corticosteroid dose and timing
  - Diverse patient populations

- Post-operative corticosteroid drug levels??
Objective

- To determine whether a standard 1mg/kg intraoperative dose of dexamethasone results in similar drug levels for all patients
- Characterize the relationship between dexamethasone levels and the innate stress response following infant CPB

Hypothesis:
Postoperative dexamethasone levels after standardized intra-operative dosing are highly variable and inversely related to the infant stress response
Eligibility

• Inclusion Criteria
  ▫ Diagnosis of Congenital Heart Disease
  ▫ Age: 0-365 days
  ▫ Planned cardiac surgery utilizing CPB

• Exclusion Criteria
  ▫ Premature Birth: < 36 weeks GA
  ▫ Corticosteroids within 24 hours before surgery
  ▫ Pre-operative mechanical circulatory support
**Congenital Heart Patients**
N=32

**Post-Induction**
- TIME 1
  - Cortisol
  - ACTH
  - IL 6,8,10

**Post-CPB Pre-MUF**
- TIME 2
  - Cortisol
  - ACTH
  - IL 6,8,10

**ICU Arrival**
- TIME 3
  - Cortisol
  - ACTH
  - IL 6,8,10

**TIME 4, 5, 6**
- Cortisol
- ACTH
- IL 6,8,10

**TIME 7**
- Cortisol
- ACTH
- IL 6,8,10

**Dex 1mg/kg**

- High Dex
  - ≥ 15 mcg/dL

- Low Dex
  - < 15 mcg/dL

*Standard fentanyl/midazolam anesthesia*

- Low Dex
  - < 15 mcg/dL
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low Dex</th>
<th>High Dex</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables</td>
<td></td>
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<tr>
<td>Age (days)</td>
<td>199 ± 114</td>
<td>225 ± 363</td>
<td>0.827</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (45%)</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>RACHS-1 score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3, n</td>
<td>18</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>4-6, n</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>104 ± 44</td>
<td>90 ± 35</td>
<td>0.35</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>51 ± 32</td>
<td>45 ± 28</td>
<td>0.63</td>
</tr>
<tr>
<td>Modified ultrafiltration (ml)</td>
<td>365 ± 192</td>
<td>293 ± 295</td>
<td>0.49</td>
</tr>
<tr>
<td>Mechanical ventilation duration (days)</td>
<td>3.9 ± 8.0</td>
<td>1.6 ± 1.4</td>
<td>1.00</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>12 ± 14</td>
<td>11 ± 11</td>
<td>0.71</td>
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</tbody>
</table>

RACHS-1 score, risk adjustment for congenital heart surgery. CPB, cardio pulmonary bypass.

Data reported as mean ± standard deviation.
Dexamethasone Levels

* denotes significant difference between groups
Cortisol Responses

*Denotes a significant difference between groups, p=0.016
High Dex and Cortisol Response

- Persistent cortisol suppression
Study Limitations

- Single center investigation
- Small sample size precludes linking cortisol levels with clinical outcomes
Conclusions

• First comparison of post-CPB dexamethasone drug levels and the infant stress response

• Dexamethasone levels vary significantly between patients after a standard pre-CPB 1 mg/kg dose
  ▫ **High and low dex responders**

• Cortisol suppression persists even after dexamethasone levels decline in high dex responders
  ▫ **Iatrogenic adrenal insufficiency??**

• Dexamethasone levels are an important variable to consider in past and future studies seeking to link cortisol response with clinical outcomes
The “Optimal” Corticosteroid Approach

• Avoid overtreatment
  ▫ Infection risk
  ▫ Adrenal suppression- “iatrogenic adrenal insufficiency”
  ▫ Glucose induction

• Avoid under suppression in “at risk” patients

• **Ultimate Goal:** To develop an individualized approach to corticosteroid mediation of the infant CPB inflammatory/stress response
Acknowledgements

Harold M. Burkhart, MD
Joseph A. Dearani, MD
William C. Oliver, Jr MD
Jamie A Kiefer, PA-C
Lucinda M Stroetz, PA-C
Frank Cetta, MD and the Mayo Clinic Dept. of Pediatric Cardiology
Mayo Clinic Cardiothoracic Clinical Nurse Anesthetists
Mayo Clinic Perfusion
DeAnna Haugen and Laurnice Olsen

Funded by:
Mayo Clinic Dept. of Pediatric and Adolescent Medicine Research Award
Small Grants Program, Mayo Clinic Div. of Cardiothoracic Surgery
Center for Translational Science Activities (CTSA) CReFF Award
Questions?
ACTH Responses

* Denotes a significant difference between groups, p=0.025
Dexamethasone Level and IL-6

- IL-8 levels were similar between groups.
- IL-10 was lower at Time 4 in High Dex group (p=0.015).
## IL-8 and IL-10

Table 3. Cytokine responses for times 1 though 7

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Low Dex</th>
<th>n</th>
<th>High Dex</th>
<th>P Value</th>
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<tr>
<td></td>
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<td>IL-8</td>
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<tr>
<td>1</td>
<td>15</td>
<td>1.33 ± 1.72</td>
<td>10</td>
<td>1.30 ± 0.62</td>
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<td>2</td>
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<td>3</td>
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<td>7.79 ± 5.11</td>
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<td>6.74 ± 4.80</td>
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<td>5</td>
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<td>3.23 ± 1.51</td>
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<td>7</td>
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<td>7.57 ± 7.49</td>
<td>5</td>
<td>2.96 ± 1.05</td>
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<tr>
<td>IL-10</td>
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</tr>
<tr>
<td>1</td>
<td>15</td>
<td>1.58 ± 3.61</td>
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<td>0.95 ± 0.78</td>
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<td>46.64 ± 27.87</td>
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<td>44.77 ± 32.13</td>
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<tr>
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<td><strong>11.96 ± 6.41</strong></td>
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<td><strong>7.14 ± 10.29</strong></td>
<td><strong>0.015</strong></td>
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<td>13.87 ± 30.87</td>
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IL, interleukin.
Potential Contributors to Drug Level Variability

- Age
- Gender
- Protein binding
- Patient genetics
- CPB related factors
Intra-Operative Steroid Practices

• Survey of Pediatric Cardiac Intensive Care Society
  ▫ 97% report intra-operative steroid use
  ▫ Only 40% use steroids with every case
  ▫ Decision for use based on:
    • Age of patient
    • Anticipated CPB time, DHCA
    • Surgeon preference

Checcia et al. Ped Crit Care Med 2005