Outcome for the neonate

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Institute of Translational Medicine
Department of Women’s and Children's Health
1. Context
2. Study #1
3. Study #2
Synaptogenesis in the mammalian cortex

Mean IQ ± 1 SD

Data from Bayerische Entwicklungsstudie (Bavarian Longitudinal Study)

Data from Epicure

(With thanks to D Wolke and N Marlow)
Study #1
Outcome of ELGAN after introduction of a revised protocol to assist preterm infants in their transition to extrauterine life

Short title: Outcome of ELGAN after gentle delivery room care

Katrin Mehler, Judith Grimme, Julia Abele, Christoph Huenseler, Bernhard Roth, Angela Kribs,
University of Cologne,
Children’s Hospital, Department of Neonatology

Acta Paediatrica; Dec 2012
Background

“Transition/Adaptation in the Delivery Room and Less RDS: Don’t Just Do Something, Stand There!”

Jobe A. Newborn and Infant Nursing Reviews, 2006; 6: 76

“First golden minutes” emphasising gentle delivery room approach for the ELGAN

Vento M et al. Neonatology 2009; 92: 286
Background

- Hypothesis: gentle delivery room management avoiding mechanical ventilation improves neonatal mortality and morbidity in ELGANS
- To investigate, delivery room management protocol revised in 2001
- “Protocol focussed on avoiding mechanical ventilation during first hours of life and on supporting preterm infants’ own vitality”
- Historical controls
Controls

- 44 infants <26w born between January 2000 and November 2001

Study group

- 164 inborn infants <26w born between November 2001 and December 2007
### Cologne 2001 - 2007

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### LWH: 2007-2010

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## Management in Delivery room and <72h

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<td>CPAP only</td>
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<td>100%</td>
<td>0</td>
<td>30%</td>
<td>0</td>
<td>50%</td>
<td>5%</td>
<td>61%</td>
<td>1%</td>
<td>55%</td>
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<tr>
<td>CPAP + surfactant</td>
<td>85%</td>
<td>0</td>
<td>72%</td>
<td>0</td>
<td>79%</td>
<td>0</td>
<td>66%</td>
<td>0</td>
<td>74%</td>
<td>0</td>
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<tr>
<td>Intubation + surfactant</td>
<td>15%</td>
<td>0</td>
<td>28%</td>
<td>60%</td>
<td>19%</td>
<td>50%</td>
<td>26%</td>
<td>33%</td>
<td>24%</td>
<td>41%</td>
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<tr>
<td>Mechanical ventilation &lt;72h</td>
<td>77%</td>
<td>50%</td>
<td>47%</td>
<td>90%</td>
<td>52%</td>
<td>66%</td>
<td>46%</td>
<td>72%</td>
<td>51%</td>
<td>72%</td>
</tr>
</tbody>
</table>
‘Revised protocol’

Prenatal

- Antenatal steroids and antibiotics; 2\textsuperscript{nd} dose after 14d
- All fetuses from 22 w
- Delivery by Caesarean section (modified Misgav Ladach method) by an experienced obstetrician
  - extraction of complete amniotic cavity containing fetus and placenta gently from uterus
- Placenta held above infant for approx 2 min; delayed cord clamping
‘Revised protocol’

Delivery room management

- Pre-warmed mattress, radiant heater and wrapped in a polyethylene cover
- Oral cavity suctioned only if blood or meconium stained amniotic fluid
- Baby received sustained CPAP via face mask with variable flow CPAP device to recruit lung volume
- Pulse oximeter to monitor heart rate and O₂ saturation
- Gas flow humidified and warmed to 38°C
‘Revised protocol’

- FiO2 initially 0.6, gas flow 15 l/min, PEEP ~8 cm H2O
  - Adjusted according to HR, resp effort, SpO2
- Gastric tube inserted after 10 min to prevent abdominal gas accumulation
‘Revised protocol’

- Target HR >100/min after 1½ min
- If HR <100/min after initiation of CPAP, flow increased by 2L/min (repeated x3 for 30 s)
- If HR <100/min after 3 min, sustained inflation (30 s) or bag and mask ventilation (repeated x3, pressure limit 25, if unsuccessful 30cm H2O)
- If HR remained <100/min, intubated
- Target SaO2 >85% after 10 min
- Intubated also if infant not breathing after gas flow increased to max 20 L/min (i.e. PEEP 14 cm H2O) and sustained inflation and/or bag and mask ventilation had been tried
‘Revised protocol’

- Criteria for surfactant application evaluated after 10min. Included:
  - clinical signs of severe dyspnoea (defined by Silverman Score >5
  - and/or FiO2 >0.3
  - and/or >15 L/min of flow to keep SaO2 >85%.

- Survanta by thin ET catheter during spontaneous breathing with CPAP at ~30 min
‘Revised protocol’

- Infants then placed in incubator and connected to infant flow nCPAP generator (EME, Brighton) or Babylog 8000 ventilator
- All intubated infants received HFOV following a high volume strategy (MAP 8-10 cm H2O, frequency 6-8Hz)

Protocol revised in 2008 after publication of studies by Wang and Escrig

- changed initial FiO2 from 0.6 to 0.3
- changed target HR from 100 to 120/min after 3 min
Conventional management during control period (1Jan 2000 - 14 Nov 2001)

- Prenatal management included antenatal steroids
- Gentle extraction with intact amniotic sac and late cord clamping not performed routinely
- Resuscitation according to ILCOR guidelines
- If infant not breathing, PPV with FiO2 0.6 applied
- HR re-evaluated after 30 seconds
Conventional management during the control period (1Jan 2000 - 14 Nov 2001)

- If HR <60/min chest compressions applied
- If HR 60-100/min PPV continued, intubation considered
- If infant breathing, stabilized with CPAP
- Infants requiring surfactant were intubated for surfactant administration and ventilated
- HFOV using high volume strategy
After admission to NICU: Conventional management

- Intubation if recurrent apnoea and bradycardia or respiratory failure (pH < 7.20 or FiO₂ > 0.5 to maintain paO₂ in range of 45-60 mmHg for >2 h)
- No strict limits for paCO₂ provided that pH ≥ 7.20
- Arterial hypotension (MAP < GA in weeks) treated if evidence of poor tissue perfusion
- All patients screened for PDA during first 48 h. PDA with L-R shunting, treated with indomethacin
• IV fluid started with 70-80ml/kg/d.

• Enteral feeding started on first day with colostrum, if available.

• Minor changes during the study period: daily protein intake raised on D1 from 1 to 3 g/kg/
Study #2

- Now a study from my own department…

- TIPIT
  - Rationale
  - Methods
  - General results
  - MRI results
A Randomised Controlled Trial of Thyroxine in Preterm Infants Under 28 weeks’ Gestation

Funder: Medical Research Council, UK
Sponsor: Liverpool Women's NHS Foundation Trust & University of Liverpool
Evidence of hypothyroxinaemia is common among infants born before 28 weeks’ gestation (69%).
### Studies of thyroid supplementation in premature babies

#### Review:
- Thyroid hormones for preventing neurodevelopmental impairment in preterm infants

#### Comparison:
- 01 Thyroid hormones versus control (All eligible studies)

#### Outcome:
- 09 Mortality to discharge

<table>
<thead>
<tr>
<th>Study</th>
<th>Thyroid hormone</th>
<th>Control</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight %</th>
<th>Relative Risk (Fixed) 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Amato 1989</td>
<td>2 / 22</td>
<td>2 / 22</td>
<td></td>
<td>6.5</td>
<td>1.00 [0.15, 6.48]</td>
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<tr>
<td>Chowdhry 1994</td>
<td>1 / 11</td>
<td>1 / 12</td>
<td></td>
<td>3.1</td>
<td>1.09 [0.08, 15.42]</td>
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<tr>
<td>Smith 2000</td>
<td>2 / 29</td>
<td>3 / 18</td>
<td></td>
<td>12.1</td>
<td>0.41 [0.08, 2.24]</td>
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<tr>
<td>Vanhole 1997</td>
<td>3 / 20</td>
<td>3 / 20</td>
<td></td>
<td>6.8</td>
<td>1.00 [0.23, 4.37]</td>
</tr>
<tr>
<td>van Wassenaer 1997</td>
<td>14 / 100</td>
<td>21 / 100</td>
<td></td>
<td>68.5</td>
<td>0.67 [0.36, 1.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>22 / 182</td>
<td>30 / 172</td>
<td></td>
<td>100.0</td>
<td>0.70 [0.42, 1.17]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.87 df=4 p=0.9291
Test for overall effect Z=-1.36 p=0.17

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Osborne 2005; Cochrane review: Thyroid hormones in preterm infants
Subgroup analysis: Van Wassanaer et al. NEJM 1997

- Developmental score for T4 group with n = 13
- Developmental score for Control group with n = 18
- Developmental score for T4 group with n = 69
- Developmental score for Control group with n = 57

p = 0.01
p = 0.03
TIPIT study

- Primary objective: To determine whether early thyroxine supplementation in infants <28w improves brain size at term equivalence

- All infants received either levothyroxine (LT4) or placebo until 32 w corrected gestational age
Primary outcome

Width of subarachnoid space as indirect measure of brain size at 36 w corrected gestational age
<table>
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<tr>
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<th>Thyroxine N = 75</th>
<th>Placebo N = 78</th>
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<tbody>
<tr>
<td>Gender (males)</td>
<td>44 (58%)</td>
<td>45 (58%)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>821 ± 184</td>
<td>842 ± 200</td>
</tr>
<tr>
<td>Gestational age (w)</td>
<td>26 ± 1.4</td>
<td>26 ± 1.3</td>
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</table>
Secondary outcome: Diffusion Tensor Imaging (DTI)

- Quantitative assessment of white matter development before myelination visible on conventional MRI by measurement of Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA)
- ADC ↓ and FA ↑ suggest water diffusing in fewer directions because of barriers to diffusion
- (The more myelinated the structure, the lower the ADC and the higher FA)
FA ADC Diffusion Direction

Red = L/R
Blue = I/S
Green = A/P
Summary of primary MRI results

LT4-supplemented (N=25) vs Placebo (N=20)

No difference for

- ADC
- FA
- Length or numbers of streamlines
Possible effects of very low or very high plasma FT4 concentrations over first 4 weeks of life

Very LOW plasma FT4 concentrations:
- Q1 vs Q2-Q4 for placebo (N = 19)

Very HIGH plasma FT4 concentrations:
- Q4 vs Q1-Q3 for LT4-supplemented (N = 23)
### Effect of low FT4: Placebo group (N=19)

<table>
<thead>
<tr>
<th></th>
<th>Q1 Mean FT4 range 1.95-6.40 pmol/L N=5</th>
<th>Q2-Q4 Mean FT4 range 6.84-25.50 pmol/L N=14</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Gestation (w)</td>
<td>24.7</td>
<td>26.4</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Birth weight (Kg)</td>
<td>0.77</td>
<td>0.89</td>
<td>p=0.04</td>
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<tr>
<td>Mortality (%)</td>
<td>50.0</td>
<td>14.6</td>
<td>p=0.01</td>
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<tr>
<td>Subarachnoid space width at 36 w CGA (Q1 vs Q2-4)</td>
<td>Mean difference +5 mm (95% CI 0.2 – 9.0)</td>
<td></td>
<td>p=0.04</td>
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</table>
Effect of low FT4: Unsupplemented group

MRI data

<table>
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<tr>
<th></th>
<th>Q1: Mean FT4 range 1.95-6.40 pmol/L N=5</th>
<th>Q2-Q4: Mean FT4 range 6.84-25.50 pmol/L N=14</th>
<th>p=0.05</th>
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<tbody>
<tr>
<td>ADC, corpus callosum</td>
<td>1.72 ±0.14</td>
<td>1.53 ±0.17</td>
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<tr>
<td>FA (Q1 vs Q2-4)</td>
<td>lower values in all eight brain regions (no sig diff)</td>
<td></td>
<td></td>
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<tr>
<td>Streamlines (Q1 vs Q2- Q4)</td>
<td>shorter and less numerous</td>
<td></td>
<td></td>
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<tr>
<td>Streamline number through right internal capsule</td>
<td>223 ±65</td>
<td>299 ±68</td>
<td>P=0.02</td>
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Effect of high FT4: LT4-supplemented (N=23)

<table>
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<th>Q1-Q3 N=17</th>
<th>Q4 N=6</th>
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<tr>
<td>ADC, left occipital lobe</td>
<td>1.78 ±0.14,</td>
<td>1.58 ±0.14</td>
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<tr>
<td>FA, anterior corpus callosum</td>
<td>0.32 ±0.05</td>
<td>0.39 ±0.03</td>
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For Q4 vs Q1-3, streamlines passing through every brain region were longer and more numerous

<table>
<thead>
<tr>
<th>Ant’r corpus callosum (No of streamlines)</th>
<th>56 ±16</th>
<th>109 ±28</th>
<th>p&lt;0.001</th>
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<tbody>
<tr>
<td>Ant’r corpus callosum (Length of streamlines)</td>
<td>23 ±6</td>
<td>35 ±5</td>
<td>p&lt;0.001</td>
</tr>
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</table>
Conclusion

- Brain MRI data suggests decreased organization of white matter for babies <28w with low plasma FT4 during first 4 w after birth

- Prospective studies of LT4-supplementation should target extremely preterm infants with very low plasma FT4 during days after birth
1. Context
2. Study #1
3. Study #2
1. Context
2. Study #1
3. Study #2