Early interventions to improve neurodevelopmental outcomes of premature infants

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Random-Effects Meta-analysis Comparing Cognitive Test Scores Between Cases and Controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>3.1 (0.5 to 5.7)</td>
</tr>
<tr>
<td>Study 2</td>
<td>2.5 (0.1 to 4.9)</td>
</tr>
<tr>
<td>Overall</td>
<td>3.0 (0.5 to 5.5)</td>
</tr>
</tbody>
</table>

Correlations Between Mean Cognitive Scores, Birth Weight, and Gestational Age

Birth weight: $R^2 = 0.51; P < 0.01$

GA: $R^2 = 0.49; P < 0.01$

Objectives

- Review recent meta-analyses on early developmental interventions
- Describe the Edmonton randomised controlled trial on NIDCAP

What is Early Intervention?

“Early Intervention consists of multidisciplinary services provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimize developmental delays, remediate existing or emerging disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning.”


Interventions post hospital discharge

- Early developmental interventions post hospital discharge to prevent motor and cognitive impairments in preterm infants

Preschool and school age outcomes

<p>| | | | | | |</p>
<table>
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www.capitalhealth.ca
Early Intervention involving parents

- Early interventions involving parents to improve neurodevelopmental outcomes of premature infants: a meta-analysis. Meta-analyses results for mental performance scores

<table>
<thead>
<tr>
<th>Age at Assessment</th>
<th>N Treatment</th>
<th>N Control</th>
<th>WMD (random) 95% CI</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>488</td>
<td>476</td>
<td>3.55 (0.05, 7.14)</td>
<td>-</td>
</tr>
<tr>
<td>12 Months</td>
<td>1207</td>
<td>1181</td>
<td>5.57 (2.39, 8.86)</td>
<td>-</td>
</tr>
<tr>
<td>24 Months</td>
<td>701</td>
<td>799</td>
<td>7.09 (5.01, 11.67)</td>
<td>-</td>
</tr>
<tr>
<td>36 Months</td>
<td>372</td>
<td>398</td>
<td>9.66 (5.01, 14.31)</td>
<td>-</td>
</tr>
<tr>
<td>5 Years</td>
<td>447</td>
<td>570</td>
<td>-1.36 (-3.84, 0.90)</td>
<td>-</td>
</tr>
</tbody>
</table>

NIDCAP improves short- and long-term outcomes for very low birth weight infants – the Edmonton randomized controlled trial

Katherine L Peters, Rhonda J. Rosychuk, Leonora Henderson, Judith J Cote, Catherine McPherson, Juzer M. Tyebkhan

What is “Developmental Care”?  

- Care that is appropriate to the developmental stage of the infant  
- Care that nurtures the infant  
- Care that supports and promotes optimal development of the infant  
- Care that considers the infant and his/her family as pivotal in interactions  
- Care that is kinder, more humane, and gentler than traditional care

What is Developmental Care?  

- Developmental care is a “Professional Alliance”, that  
  - supports the parent’s engrossment with the child,  
  - supports the child’s neurobiological expectations of nurture,  
  - that listens to the child [via his/ her behaviour] - [NIDCAP specific]  
  - uses this behavioural dialogue to guide the care - [NIDCAP specific]  
  - from Dr Heidelise Als
What is NIDCAP?

- Newborn Individualized Developmental Care and Assessment Program
- framework for family-centered developmentally supportive care
- formalized naturalistic observations
- care plans for individualized care

The Synactive Theory

- The Synactive Theory of Development; [Dr Heidelise Als]
  - How an infant’s neurobehavioural systems develop
  - The interaction between the systems
  - The interaction of the systems with the environment

NIDCAP

- NIDCAP teaches care givers how to assess the stability of these subsystems and to be sensitive to the subtle cues of stress, of each subsystem
- NIDCAP based care helps to support the stability of these subsystems, within an environment as near as possible to being in utero
- Effects of early postnatal experience on the developing brain

The Synactive Theory

Environment → Attention - Interaction
Self Regulation → Sleep- wake
Motor → Autonomic
Edmonton Randomized Controlled Trial of NIDCAP

Objective

- To determine the impact of NIDCAP-based care on outcomes in VLBW infants in a two-phase cluster RCT

Primary outcome – length of hospital stay

- Environment - "nurturing, loving home"
- Self Regulation - all subsystems integrated
- Attention - Interaction - communicates with parents
- Sleep-wake cycles - wakes for feeds, interact
- Motor - able to demand feed and gain weight
- Autonomic - regulates temperature, no apneas or bradycardias, no feeding intolerance

Secondary outcomes

- Ventilation days
- CPAP days
- Supplemental oxygen days
- Chronic lung disease
- Neurodevelopmental outcomes at 18-months adjusted age
This study had 2 phases

- PHASE I [May 1998 – September 1999]
  - Staff education in NIDCAP

- PHASE II [September 1999 – September 2004]
  - RCT of NIDCAP based care in the NICU and neurodevelopmental follow-up
  - Institutional ethics approval obtained

Inclusion criteria

- Birth weight 500 - 1250 g
- Gestational age ≤ 32 weeks
- Birth weight 3 - 97 % for gestational age
- Survival to at least 48 hours of life
- Enrolled by 7 days of age
- Parent(s) speak a language spoken by one of the NIDCAP staff
- Twins - eligible if BOTH met inclusion criteria; randomised to the same group

Exclusion criteria

- Chromosomal or major congenital anomalies
- Maternal alcohol or drug use in pregnancy
- Known congenital infection
- Decision, or discussion started, re: withdrawal of intensive care treatments before 48 hours of life

Randomisation

- Computer generated random numbers without blocking
- After parental consent obtained, sealed sequentially numbered envelope was opened and infant entered into the appropriate group
- Enrollment: Sept 1999 and Dec 2002
Intervention

- Intervention under investigation =
  - “Care given by nursing staff with education in
    NIDCAP, assisted by behavioural
    observations and care plans performed by
    NIDCAP certified staff”
  - At least 50% of nursing care for the NIDCAP
    group must be by NIDCAP educated nurses

- Control infants
  - usual standard of nursery care
  - no care from NIDCAP educated nurses, no
    “NIDCAP” behavioural observations or
    “NIDCAP” care plans

Intervention

- Medical care was directed by the neonatologist
  on service, assisted by NNP’s and fellows
  training in Neonatology
  - Only 3 out of 26 neonatologists, NNP’s and
    fellows were NIDCAP certified
  - Suggestions for medical care were made to
    clinical team by NIDCAP physicians / NNP if
    appropriate

Primary Outcome - Length of stay

- Infants transferred to other Level II nursery if
  - Nearer family home
  - Study site nursery full / staffing crisis
  - Off CPAP /Hi Flow O2 /TPN
  - Prospectively followed by telephone calls to
    each peripheral hospital every 1 to 2 weeks
Primary Outcome - Length of stay

• Decision to discharge infant according to standard practice of the respective hospitals in our region
  • May be on methylxanthines, oxygen
  • Not tube fed
• Decision to discharge made by attending physicians with nursing input
  • approximately 45 pediatricians

Primary Outcome - Length of stay

• Number of calendar days in hospital

Secondary outcomes

• Days of ventilation = any day, when mechanical ventilation was required

• Days of CPAP = any day when CPAP was required, but not including days where both ventilation and CPAP were required. High Flow oxygen = CPAP

Secondary outcomes

• Days of Oxygen = any day where supplemental oxygen was required, but not including days where ventilation and/or CPAP were also required

• Chronic Lung Disease = need for supplemental oxygen to maintain oxygen saturation 92 - 96 %, at a post conceptual age of 36 weeks
Secondary outcomes

- 18-month follow-up
- Disability
  - Cerebral palsy of any type or severity
  - Visual impairment (corrected visual acuity in the better eye < 20/60)
  - Binaural/bilateral sensorineural hearing loss > 40dB at any frequency 250-4000Hz
- Mental delay (BSID-II)
  - Moderate mental delay < 70
  - Severe mental delay < 55

Statistical Analyses

- Intention to treat
- Descriptive statistics for infant and maternal data
- Two-sample t-tests or Wilcoxon rank–sum tests
- Chi Square or Fisher’s Exact test
- Kaplan Meier curves and Cox proportional hazards regression techniques
- Multivariable proportional hazards models developed for Length of Stay
- Splus
- P of <0.05 significant

Sample size

- Sample size, to achieve a realistic reduction in LOS by 15%, from a median of 85 days to 72 days,
  - with α of 5%,
  - and power of 0.8
  
  = 110 infants, [55 per group]
# Results - Study Intervention

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 56</td>
<td>n = 55</td>
<td></td>
</tr>
<tr>
<td>nursing</td>
<td>83 %</td>
<td>0 %</td>
</tr>
<tr>
<td>[% of total nursing time]</td>
<td>49 - 95</td>
<td>0 - 27</td>
</tr>
<tr>
<td>care plans</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>[median and range]</td>
<td>1 - 7</td>
<td>0</td>
</tr>
</tbody>
</table>

# Results – Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>N = 55</th>
<th>C = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age [yrs]</td>
<td>27.4</td>
<td>26.6</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Blishen</td>
<td>42.1</td>
<td>42.7</td>
</tr>
<tr>
<td>Antenatal steroids [%]</td>
<td>82</td>
<td>89</td>
</tr>
<tr>
<td>Inborn [%]</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>Cesarean section [%]</td>
<td>55</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N = 60</th>
<th>C = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age [wks]</td>
<td>27.5</td>
<td>27.0</td>
</tr>
<tr>
<td>Birth weight [g]</td>
<td>988.2</td>
<td>927.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N = 60</th>
<th>C = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male [%]</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Apgar 5 minutes</td>
<td>7.3</td>
<td>7.3</td>
</tr>
<tr>
<td>SNAPPE-II score</td>
<td>22.7</td>
<td>26.4</td>
</tr>
<tr>
<td>SNAPPE-II pred mortality [%]</td>
<td>7.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Age at randomization [d]</td>
<td>4.1</td>
<td>4.1</td>
</tr>
</tbody>
</table>
## Results – Neonatal clinical course

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants</td>
<td>47/60 (78%)</td>
<td>43/60 (72%)</td>
</tr>
<tr>
<td>Ventilator support</td>
<td>47/60 (78%)</td>
<td>43/60 (72%)</td>
</tr>
<tr>
<td>Surfactant in ventilated infants</td>
<td>36/47 (77%)</td>
<td>35/43 (81%)</td>
</tr>
<tr>
<td>Inotrope use*</td>
<td>18/60 (30%)</td>
<td>29/60 (48%)</td>
</tr>
</tbody>
</table>

* P = 0.05

## Results – Neonatal clinical course

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVH with VM and/or IPED</td>
<td>2/56 (4%)</td>
<td>1/55 (2%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>20/56 (36%)</td>
<td>23/55 (42%)</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>6/56 (11%)</td>
<td>12/54 (22%)</td>
</tr>
<tr>
<td>Methylxanthine use</td>
<td>56/56 (100%)</td>
<td>54/55 (98%)</td>
</tr>
<tr>
<td>Dexamethasone use</td>
<td>4/56 (7%)</td>
<td>7/55 (13%)</td>
</tr>
</tbody>
</table>

## Results - Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 56 n = 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS [d]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>75.5</td>
<td>90.2</td>
</tr>
<tr>
<td>Median</td>
<td>71.5</td>
<td>84.0</td>
</tr>
<tr>
<td>Range</td>
<td>40-126</td>
<td>32-169</td>
</tr>
</tbody>
</table>

*p = 0.003

## Length of stay in hospital by group

![Graph showing length of stay in hospital by group](#)
### LOS: Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Est</th>
<th>SE</th>
<th>p-value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDCAP</td>
<td>0.501</td>
<td>0.229</td>
<td>0.029</td>
<td>1.65</td>
<td>(1.05, 2.59)</td>
</tr>
<tr>
<td>GA</td>
<td>0.478</td>
<td>0.082</td>
<td>&lt;0.001</td>
<td>1.61</td>
<td>(1.37, 1.89)</td>
</tr>
<tr>
<td>log(PredMort)</td>
<td>-0.294</td>
<td>0.100</td>
<td>0.003</td>
<td>0.75</td>
<td>(0.61, 0.91)</td>
</tr>
<tr>
<td>Vent at Rand (Y/N)</td>
<td>-0.976</td>
<td>0.311</td>
<td>0.002</td>
<td>0.38</td>
<td>(0.21, 0.69)</td>
</tr>
<tr>
<td>VentDays at Rand</td>
<td>-0.221</td>
<td>0.103</td>
<td>0.032</td>
<td>0.80</td>
<td>(0.66, 0.98)</td>
</tr>
<tr>
<td>Male</td>
<td>-0.471</td>
<td>0.228</td>
<td>0.062</td>
<td>0.62</td>
<td>(0.40, 0.98)</td>
</tr>
</tbody>
</table>

### Results - Respiratory outcomes

#### N C

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 19</td>
<td></td>
<td>n = 26</td>
</tr>
</tbody>
</table>

**Vent’n [d]** – survivors only, ventilated at randomization

- **Mean**
  - 14.7
  - 31.0

- **Median**
  - 12
  - 24

- **Range**
  - 0-47
  - 0-103

* p = NS

### Respiratory outcomes

- **NC**
  - n = 56
  - n = 55

#### Survivors only

<table>
<thead>
<tr>
<th>Days CPAP</th>
<th>Days O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.0</td>
<td>13.5</td>
</tr>
<tr>
<td>28.1</td>
<td>15.2</td>
</tr>
</tbody>
</table>

* no significant difference between groups

### CLD [%]

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<tr>
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<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 56</td>
<td></td>
<td>55</td>
</tr>
</tbody>
</table>

- **All survivors**
  - 16/56 (29%)
  - 27/55 (49%)

- **Vent’d survivors**
  - 16/43 (38%)
  - 25/38 (66%)

* P = 0.04
OR 0.42, 95% CI 0.18 to 0.95

* P = 0.01
OR 0.31, 95% CI 0.12 to 0.77
### 18-month outcomes

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 51  n = 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any disability*</td>
<td>5 (10%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>MDI &lt; 70*</td>
<td>5 (10%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Mean MDI</td>
<td>85.1 ± 15.3</td>
<td>79.5 ± 18.3</td>
</tr>
</tbody>
</table>

*P = 0.017

OR 0.25, 95% CI 0.08 - 0.82

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### Conclusions

- NIDCAP based care significantly reduced
  - the mean length of hospital stay by 15 days
  - the incidence of chronic lung disease
  - neurodevelopmental disability, specifically mental delay

---

### Developmental Care in NICU

Our logo represents an infant’s levels of behavioral functioning, supported by parental participation in care.  

Edmonton Developmental Care
**Strengths**

- Largest RCT to date – adequate power to prove our primary hypothesis
- Majority of infants received antenatal corticosteroids and surfactant
- Follow-up to 18-months
- Outcomes available for > 90% of infants

**Limitations**

- Unblinded intervention
- Volunteer bias
- N patients no longer received NIDCAP-based care after transfer to other sites

**Acknowledgements**

- Alberta Heritage Foundation of Medical Research
- Canadian Lung Association: Canadian Nurses Respiratory Society
- Alberta Lung Association
- Perinatal Clinical Research Centre, University of Alberta
- Neonatal Research Trust Fund

**With thanks to…**

- Nursing staff who volunteered to do NIDCAP education
- Our colleagues on the NICU - nursing, medical, respiratory, OT, nutrition, social work, pharmacy, administration,
- Neonatal Research Office
With thanks to….

- Dr Philip Etches and Dr John Van Aerde, Medical Directors
- Jean Gardner Cole, NIDCAP Trainer
- Neonatal and Infant Follow-up Clinic, Glenrose Rehabilitation Hospital
  - Dr. Charlene Robertson

With special thanks to

- All the babies and their families who participated in this study

Finally…

- Early interventions improve neurodevelopmental outcomes of preterm infants
- This form of care giving is kinder, more humane, and gentler than traditional care
- If this was ME, or MY CHILD, what kind of care giving would I want?
  - [Juzer’s bedside definition]