Non Invasive Ventilation for the Premature Infant

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Disclosures

I receive support from the US government for work in neonatal clinical pharmacology, clinical trials, and cohort studies including:

1. FDA R01 FD005101, PI Laughon
2. NHLBI R34 HL124038, PI Laughon
3. NIH Office of the Director ECHO Coordinating Center U2C OD023375, PI Smith, Duke
4. NICHD Pediatric Trials Network Government Contract HHSN267200700051C, PI Benjamin, Duke
5. Satellite site PI for the NICHD Neonatal Research Network NICHD U10 HD040492, PI Cotten, Duke

Industry: Astellas, Cempra, Medipost, Abbvie for DSMBs and consulting
I intend to discuss an unapproved/ investigative use of a commercial product/device in my presentation.
Clinical Case

- 25 1/7 weeks
- Mother has been in hospital for 2 weeks for preeclampsia
- Received 2 doses of betamethasone
- Develops HELLP
- Resuscitation team called: we will deliver (via cesarean) soon

Real time simulation

A. Intubate, provide surfactant, mechanical ventilation
B. Intubate, provide surfactant, extubate
C. CPAP with a face mask then NCPAP
D. NCPAP
E. NIPPV
Principles of NIV

- Avoid mechanical ventilation
- Maintain functional residual capacity (FRC)
- Technical aspects

“Iron lung” or Drinker Respirator

wikipedia
Iron Lung: Clinical Case

- Late 60s
- 1952: contracted polio at age 6
- As of 2015, still living in iron lung
- 3 degrees, including law


Mechanical ventilation and lung injury

Attar and Donn. Seminars. 2006.
Gregory: premature infant NCPAP


Bubble NCPAP

Fisher and Paykel
NCPAP: How it works

• Splints upper airway
  » Reduces obstruction
  » Maintains airway patency
  » Reduces airway resistance

• Recruits alveoli/prevents collapse
  » Maintains FRC and lung volumes
    • Reduces VQ mismatch
    • Decrease WOB
  » Promotes surfactant

https://www.acltest.org/pediatric-vs-adult-airway/
http://www2.hawaii.edu/~yzuo/research1-surfactant.html

Technical aspects

• Know your unit’s device and interface!
  » “Buy in” from personnel

• Device
• Interface
• Infant characteristics
  » Mouth, nose, disease state
• Heat
• Humidity

• Synchronization
Types of NIV

- NC
- HFNC
  - HHFNC
- NCPAP
- NIPPV
  - Synchronized or not
  - NIV NAVA

NAVA

- Neurally adjusted ventilatory assist
  - Invasive and non-invasive
- Edi Catheter
  - Embedded sensors
- Synchronizes with spontaneous breaths
- Adjust amount of support
- Apnea delay

https://www.maquet.com/int/products/nava
Flow Generators

Fisher and Paykel; Hamilton Medical; Drager

Nasal Interface
**Patient Factors**

- Weight
- Gestational age
- Postnatal age
- Nares
- Mouth
- Disease
  » RDS vs. BPD

**Risks**

- Nasal septal injury
- NEC
- GI perforation
- Pneumothorax

Goldstein and Gitman. Neoreviews. 2015
NIV: when to use

- Delivery Room
- Extubation

- Short term goal: avoid mechanical ventilation
- Longer term goal: Reduce incidence of important neonatal morbidities including BPD

Clinical Case

- 25 weeks, 1 day gestational age
- Infant delivers
- Delayed cord clamping
- Spontaneously breathing, HR >100
- Apgars 6, 8
- 7 minutes after birth: CPAP +5, FiO2 0.30
Management

A. Intubate, provide surfactant, place the infant on mechanical ventilation
B. Intubate with ETT, provide surfactant, and extubate (INSURE)
C. Intubate with feeding tube, provide surfactant, and extubate (LISA)
D. Surfactant? That's a bad word. Put her on NCPAP!
E. NIPPV

NIPPV vs. NCPAP

• Reduces “need” for mechanical ventilation in first postnatal week
NIPPV vs. NCPAP: “respiratory failure”

NIPPV vs. NCPAP: BPD

Cochrane Database of Systematic Reviews
15 DEC 2016 DOI: 10.1002/14651858.CD005384.pub2

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Devices: Variability

- **NCPAP**
  - Sindi driver
  - Infant star
    - Short and long
  - Infant Flow Driver (EME)
  - Bear Cub/Viasys

- **NIPPV**
  - Babylog 8000
  - Infant star with capsule
    - Short and long
  - Newport, Teama, Stephan, Millenium
  - Bear cub

Population and “failure”: variability

**Population**
- Mean BW 831, 963, 1250
- Postnatal age 8 days to 3 weeks
- GA 25-35 weeks

**Extubation “failure”**
- pH <7.25
- PCO2 >60, >70
- “Frequent apnea”, >6 per 24 hours; 1 or 2 with PPV
- FiO2 >0.6, >0.7
- FiO2 increased >0.25
NIPPV vs. NCPAP: Conclusions

- Overall, reduces mechanical ventilation.
- No difference in other morbidities of prematurity, including BPD.
- Synchronicity did not appear to make a difference.
- Wide range of devices; “lumpers” vs. “splitters”.

NCPAP vs. Surfactant
NCPAP vs. Surfactant: Death or BPD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Avoid ventilation</th>
<th>Control group</th>
<th>Weight, %</th>
<th>Odds Ratio</th>
<th>MNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BPD/death Total</td>
<td>BPD/death Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OGIN (2009)</td>
<td>109</td>
<td>307</td>
<td>122</td>
<td>303</td>
<td>19.8</td>
</tr>
<tr>
<td>CNBH (2009)</td>
<td>53</td>
<td>74</td>
<td>54</td>
<td>72</td>
<td>4.0</td>
</tr>
<tr>
<td>SUPPORT (2010)</td>
<td>533</td>
<td>651</td>
<td>353</td>
<td>653</td>
<td>45.5</td>
</tr>
<tr>
<td>CUREPAP (2010)</td>
<td>72</td>
<td>103</td>
<td>23</td>
<td>105</td>
<td>4.8</td>
</tr>
<tr>
<td>DMM (2011)</td>
<td>68</td>
<td>223</td>
<td>128</td>
<td>429</td>
<td>17.4</td>
</tr>
<tr>
<td>AMV (2011)</td>
<td>15</td>
<td>108</td>
<td>17</td>
<td>112</td>
<td>3.8</td>
</tr>
<tr>
<td>Take Care (2013)</td>
<td>25</td>
<td>74</td>
<td>30</td>
<td>67</td>
<td>4.6</td>
</tr>
<tr>
<td>Total</td>
<td>614</td>
<td>1552</td>
<td>737</td>
<td>1737</td>
<td>100</td>
</tr>
</tbody>
</table>

Test for overall effect: $z = 2.55 (P = .01)

Heterogeneity: $\hat{\tau}^2 = 0.00; \chi^2 = 1.27; df = 6 (P = .97); I^2 = 4%$

Favors avoiding ventilation: 1
Favors control group: 20


JAMA Users’ Guides to the Medical Literature

- Chapter 7: Therapy (Randomized trials)
  - Were the Study Patients Similar to the Patient in My Practice?
  - Generalizability

- http://jamaevidence.mhmedical.com
Generalizability: COIN

- Antenatal consent
- Inclusion:
  - 25-28 weeks GA
  - Ability to breathe at 5 minutes but needing respiratory support
- Exclusion
  - Intubated before randomization
  - Required no respiratory support or oxygen


COIN: Enrollment (Figure 1)

- 2165 infants 25-28 weeks
  - 1549 not enrolled
    - 60 consented but not randomized
    - 1489
      - 418 reason not stated
      - 411 insufficient time before delivery
      - 301 did not meet inclusion criteria
    - 233 refused consent
    - 126 not approached
- 616 randomized

SUPPORT: NCPAP vs. surfactant

- Pilot study: all infants at 23 weeks intubated
- Antenatal consent

**TABLE 1** Demographic Information for Randomly Assigned Versus Nonenrolled Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enrolled (N = 1316)</th>
<th>Nonenrolled (N = 3053)</th>
<th>Unadjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (wk) (mean ± SD)</td>
<td>26.2 ± 1.1</td>
<td>26.0 ± 1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight (g) (mean ± SD)</td>
<td>830.1 ± 193.2</td>
<td>812.5 ± 191.8</td>
<td>.006</td>
</tr>
<tr>
<td>Male</td>
<td>54.1%</td>
<td>52.6%</td>
<td>.373</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>39.6%</td>
<td>36.1%</td>
<td>.350</td>
</tr>
<tr>
<td>Prenatal antibiotics</td>
<td>78.1%</td>
<td>65.4%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ANS (any)</td>
<td>96.2%</td>
<td>84.4%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ANS (full course)</td>
<td>71.7%</td>
<td>49.4%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>


**TABLE 2** Delivery Room Status and Interventions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enrolled (N = 1316, %)</th>
<th>Nonenrolled (N = 3053, %)</th>
<th>Unadjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar &lt;3 at 1 min</td>
<td>24.4</td>
<td>31.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apgar &lt;3 at 5 min</td>
<td>4.4</td>
<td>8.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intubated in DR</td>
<td>63.6</td>
<td>75.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surfactant in DR or NICU</td>
<td>82.5</td>
<td>86.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chest compressions in DR</td>
<td>5.9</td>
<td>9.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Epinephrine in DR</td>
<td>3.1</td>
<td>6.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**TABLE 3** Neonatal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SUPPORT Enrolled (N = 1316)</th>
<th>Nonenrolled (N = 3053)</th>
<th>Unadjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>18.0%</td>
<td>24.1%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BPD (oxygen at 56 wk)</td>
<td>42.2</td>
<td>47.7</td>
<td>.003</td>
</tr>
<tr>
<td>BPD or death by 36 wk</td>
<td>51.4</td>
<td>59.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ROP (surgery or retinal detachment)</td>
<td>10.4</td>
<td>12.4</td>
<td>.101</td>
</tr>
<tr>
<td>NEC (medical or surgical)</td>
<td>11.3</td>
<td>12.7</td>
<td>.214</td>
</tr>
<tr>
<td>IVH grade 3–4</td>
<td>15.0</td>
<td>17.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PVL</td>
<td>3.8%</td>
<td>5.1%</td>
<td>.608</td>
</tr>
<tr>
<td>IVH 3–4 or PVL</td>
<td>15.1%</td>
<td>19.8%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death or IVH 3–4 or PVL</td>
<td>27.4%</td>
<td>35.6%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NCPAP vs. surfactant, conclusions

- Infants can be supported with NCPAP alone without mechanical ventilation.
  - ? Less use of resources
  - Incidence of morbidities similar (from trials)
- "Buy in" from personnel
- Infants enrolled in trials may be similar or dissimilar to individual infants in the "general NICU population"

Current (future?) technologies

- "Biphasic Cuirass Ventilation"
- “…automagically compensate for leaks…”

http://www.hayekmedical.com/
Clinical Case

- Placed on NCPAP alone
- Develops increase WOB, intubated at 18 hours, surfactant
- Mechanical ventilation for 5 days; ready to be extubated?

Management

A. Administer caffeine, extubate to NCPAP
B. Administer caffeine, extubate to NIPPV
C. ? Caffeine, we started that on day 0. Extubate to NCPAP
D. No way this infant will remain extubated, leave her on the ventilator for another week
NIPPV vs. NCPAP for extubation

- Cochrane: 10 trials 1431 infants
- Reduces extubation failure 48 hours to one week
  » RR 0.76 (0.65-0.88)
- Synchronize vs. nonsynchronous: no difference


NIPPV vs. NCPAP: BPD/CLD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NIPPV</th>
<th>NCPAP</th>
<th>Risk Ratio (95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrington 2001</td>
<td>1027</td>
<td>1527</td>
<td>0.74 (0.47, 1.17)</td>
<td>7.4 %</td>
<td>0.74 (0.47, 1.17)</td>
</tr>
<tr>
<td>January 2014</td>
<td>205</td>
<td>28</td>
<td>4.75</td>
<td>0.5 %</td>
<td>0.52 (0.28, 0.95)</td>
</tr>
<tr>
<td>Hollie 2001</td>
<td>1314</td>
<td>1810</td>
<td>0.74</td>
<td>6.3 %</td>
<td>0.68 (0.56, 0.84)</td>
</tr>
<tr>
<td>Hoekstra 2013</td>
<td>144/56</td>
<td>130/59</td>
<td>0.95</td>
<td>1.7 %</td>
<td>0.95 (0.86, 1.06)</td>
</tr>
<tr>
<td>Hornik 2000</td>
<td>950</td>
<td>731</td>
<td>3.08</td>
<td>5.4 %</td>
<td>0.08 (0.01, 0.55)</td>
</tr>
<tr>
<td>Gomma 2012</td>
<td>2154</td>
<td>2294</td>
<td>10.95</td>
<td>0.5 %</td>
<td>0.62 (0.52, 1.03)</td>
</tr>
</tbody>
</table>

Total (550-589) 580 580 100.0% 0.54 (0.80, 1.19)

Favours NIPPV

Cochrane Database of Systematic Reviews
1 Feb 2017. DOI: 10.1002/14651858.CD003212.pub3
Conclusions

- Mechanical ventilation (through endotracheal tube) is injurious
  » Avoiding mechanical ventilation is a laudable goal
- NCPAP (and NiPPV) can avoid mechanical ventilation
  » Whether in the delivery room or to facilitate extubation
  » Devices and strategies vary widely
  » Possible (likely?) that the optimum strategy will be developed
- Know one’s population, devices, and approach
Questions?
Clinical Case

- Mother with no prenatal care presents to outside hospital with ROM and intermittent contractions
- Transferred to tertiary care hospital
- Ultrasound estimate is 23-24 weeks
- 540 g
NIPPV vs. NCPAP: Need for mechanical ventilation

<table>
<thead>
<tr>
<th>Study and group</th>
<th>NIPPV n (%)</th>
<th>NCPAP n (%)</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Weight</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Stage mean groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baldigian 2001</td>
<td>57/110</td>
<td>56/109</td>
<td>0.5</td>
<td>0.38-0.62</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Work 2001</td>
<td>189/110</td>
<td>193/109</td>
<td>0.8</td>
<td>0.65-0.94</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Model 2001</td>
<td>204/132</td>
<td>207/129</td>
<td>0.9</td>
<td>0.79-1.07</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Gas 2010</td>
<td>8/83</td>
<td>9/86</td>
<td>0.8</td>
<td>0.52-0.96</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Ohkura 2013</td>
<td>156/403</td>
<td>162/422</td>
<td>1.0</td>
<td>0.86-1.16</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1393/1238</td>
<td>1401/1240</td>
<td>0.9</td>
<td>0.87-1.01</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>639/636</td>
<td></td>
<td>0.9</td>
<td>0.79-1.03</td>
<td>0.73</td>
<td>0.83-1.04</td>
</tr>
<tr>
<td>Study and group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Stage mean difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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