COULD AUTOMATED CONTROL OF OXYGEN LEVELS IMPROVE SURVIVAL AND REDUCE NEC?

Eduardo Bancalari MD
University of Miami Miller School of Medicine
Jackson Memorial Medical Center
Sydney 2016

Disclosure

The University of Miami, Drs. Claure and Bancalari have a patent on the algorithm for automated adjustment of inspired oxygen and a licensing agreement with Carefusion.

Clio studies have been supported by Carefusion.

Oxygen Dependency

Infants born at UM-JMH, GA 24-31w Years 2008-2009

Supplemental Oxygen for Preterm Infants: A Very Tight Balance

CNS damage
Multi organ failure:
   GI/NEC, Renal
   CV/PDA, PH
Impaired growth
Increased mortality

Too Little

Eye damage-ROP
CNS damage
Lung injury-BPD
Oxidative stress
Increased mortality?

Too Much

Restricted (85-89) vs. Liberal (91-95) Oxygen Exposure

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>RR (95% CI)</th>
<th>Participants</th>
<th>Q of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death to discharge</td>
<td>1.18 (1.03-1.36)*</td>
<td>3757</td>
<td>Low</td>
</tr>
<tr>
<td>Death – 24 mo</td>
<td>1.16 (0.98-1.37)</td>
<td>2783</td>
<td>Moderate</td>
</tr>
<tr>
<td>Death/Disability</td>
<td>1.02 (0.94-1.14)</td>
<td>2716</td>
<td>Moderate</td>
</tr>
<tr>
<td>BPD</td>
<td>0.95 (0.87-1.04)</td>
<td>2869</td>
<td>Moderate</td>
</tr>
<tr>
<td>NEC</td>
<td>1.24 (1.05-1.47)*</td>
<td>4929</td>
<td>Moderate</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>0.72 (0.5-1.04)</td>
<td>4066</td>
<td>Low</td>
</tr>
</tbody>
</table>

From Manja et al JAMA Pediatrics 2015

Oxygen Saturation Target Range for Extremely Preterm Infants

Achieved Versus Intended Pulse Oximeter Saturation in Infants Born Less Than 28wks
The AVIOx Study

14 Centers using different saturation targets

<table>
<thead>
<tr>
<th>Percent time</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Below target</td>
<td>16 (0-47)</td>
</tr>
<tr>
<td>Within target</td>
<td>48 (6-75)</td>
</tr>
<tr>
<td>Above target</td>
<td>36 (5-90)</td>
</tr>
</tbody>
</table>

Hagadorn et al. Pediatrics 2006

Why are we so bad in keeping oxygen targets?

- Blood oxygen level fluctuates constantly: Require close attention and tight alarm settings
- Delayed response:
  - Lack of buy-in by staff, unknown consequences of transient deviations
  - Desensitization to frequent alarms
- More concern with hypoxemia than hyperoxemia
- Response is not always the most appropriate for the cause of the hypoxemia

Manual FiO2 adjustments

How can oxygen target be improved?

- Implementing clear guidelines for oxygen monitoring and targets
- Setting alarms on or close to target range
- Minimizing factors that induce fluctuations in oxygenation
- Continuous education of medical and nursing personnel
- Proper nurse patient ratio
- Monitoring compliance with oxygen targets
- Automated systems for oxygen control
Automated Adjustment of Inspired Oxygen in Mechanically Ventilated Preterm Infants: A Multicenter Crossover Trial

Claure et al Pediatrics 2010

- The study consisted of 2 consecutive periods:
  - 24 h with FiO2 adjusted as done routinely by clinical staff (Standard)
  - 24 h of automated FiO2 adjustment (Automated)
- The sequence was assigned at random in blocks by center
- The intended SpO2 range for both Automated and Standard periods was 87 - 93%

32 infants were included in the analysis:
- Birthweight: 671 ± 156 grams
- Gestational age: 25 ± 2 weeks
- Postnatal age: 26 ± 15 days

Clio

Proportional-integral-derivative controller (PID controller).

To determine what FiO2 should be delivered the algorithm responds to:
- The difference between the target and actual SpO2
- The rate at which the SpO2 is changing
- The range the patient is in (hyperoxemic, normoxemic or hypoxemic) as defined by the set high and low SpO2 targets
- How long the actual SpO2 is "out of range"
Hourly SpO2 and FiO2

Hourly SpO2 and FiO2

Claure et al.  Pediatrics 2010

Workload: FiO2 adjustments

Workload: FiO2 adjustments

* p<0.001 Paired t-test (mean±SD)

Claure et al.  Pediatrics 2010

Conclusions

Automated FiO2 adjustment

- Improved maintenance of SpO2 within intended range
- Reduced hyperoxemia and supplemental O2
- Reduced hypoxemia episodes
- Increased number of mild episodes of SpO2 below the intended range, likely due to FiO2 weaning and avoidance of hyperoxemia
- Reduced staff workload

There were no study related adverse events

IMCS CLIO2

<table>
<thead>
<tr>
<th></th>
<th>Non-invasive</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FiO2-A</td>
<td>FiO2-M</td>
</tr>
<tr>
<td>% time in target</td>
<td>60±17</td>
<td>54±15  *</td>
</tr>
<tr>
<td>% time above target</td>
<td>23±14</td>
<td>23±10</td>
</tr>
<tr>
<td>% time below target</td>
<td>17±10</td>
<td>23±8   *</td>
</tr>
<tr>
<td>% time SpO2&lt;98%</td>
<td>0.5 (0.2-1.7)</td>
<td>1.2 (0.6-2.5) *</td>
</tr>
<tr>
<td>SpO2&lt;98%, &gt;1 min, n/24h</td>
<td>3 (0-10)</td>
<td>9 (2-17) *</td>
</tr>
<tr>
<td>% time SpO2&lt;90%</td>
<td>1.3 (0.3-1.9)</td>
<td>2.5 (1.4-4.3) *</td>
</tr>
<tr>
<td>SpO2&lt;90%, &gt;1 min, n/24h</td>
<td>5 (1-10)</td>
<td>13 (7-24) *</td>
</tr>
</tbody>
</table>

From Van Kaam A et al. J Pediatr 2015

Long episodes of hypoxemia during Manual and Auto FiO2 control

<table>
<thead>
<tr>
<th>SpO2 target range</th>
<th># of episodes / 24 h</th>
<th>Manual mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Auto</td>
<td>Manual</td>
</tr>
<tr>
<td>Claure, 2009 88 - 95%</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Claure, 2011 87 - 93%</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>Waitz, 2014 88 - 96%</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Lal, 2014 90 - 95%</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Van Kaam, 2014 89 - 93%</td>
<td>4</td>
<td>15</td>
</tr>
</tbody>
</table>

From Van Kaam A et al. J Pediatr 2015
Limitations of automatic FiO2 control

- Like manual control automated FiO2 control is dependent on accuracy of pulse oximeter
- Observed differences are relative to the effectiveness of the standard of care
- Can produce more fluctuations in inspired oxygen levels and saturation
- FiO2 change is not always the most appropriate intervention (e.g. in hypoventilation)
- Automated FiO2 may give false sense of confidence and reduce attentiveness

Could automated control of oxygen levels improve survival, reduce NEC, ROP and NDI?

- Exposure to hyperoxia and hypoxia are associated with increased ROP and NDI
- Lower SpO2 targets are associated with increased mortality and NEC
- Automated FiO2 control increases time on target and reduces prolonged episodes of hyper and hypoxemia
- Definitive answer to these questions will come only from RCT exploring long term use of automated oxygen control on relevant outcomes