Lung Protective Mechanical Ventilation in Pediatric Acute Respiratory Distress Syndrome

Study by PACCMAN collaboration
Background

• Acute respiratory distress syndrome (ARDS) is recognized as the most severe form of lung injury with oxygenation failure

• The only available treatment is supportive MV

• MV in itself has the potential to initiate and aggravate lung injury

• Led to development of lung-protective mechanical ventilation (LPMV) strategies which aim to minimize ventilator induced lung injury
Background

• PARDS mortality in Asia (30%) is higher than global mortality rates (17%)

• Pediatric Acute Lung Injury Consensus Conference (PALICC) recommendations were developed in 2015

• Compliance to recommendations is poor:
  • 25% with PIP>28cmH2O
  • >75% with TV>6ml/kg
  • >50% do not observe permissive hypoxia
  • >50% do not observe permissive hypercarbia

• Could this account for the high mortality rate?
Aims and Hypothesis

• **Aim 1**: to determine if a pragmatic LPMV protocol applied to patients with PARDS over the first 7 days of disease reduces mortality

• **Hypothesis 1**: LPMV deployed in the form of a pragmatic ventilation protocol in the first 7 days of PARDS reduces mortality by one-third
Aims and Hypothesis

• **Specific aim 2**: To determine if the level of adherence to LPMV elements is greater after the implementation of the LPMV protocol

• **Hypothesis 2**: The level of adherence to LPMV elements in the first 7 days of PARDS as measured by an adherence score, is greater after the implementation of the LPMV protocol
Aims and Hypothesis

• **Specific aim 3:** To determine if the level of adherence to LPMV elements applied to patients with PARDS over the first 7 days of disease reduces mortality

• **Hypothesis 3:** The level of adherence to LPMV elements in the first 7 days of PARDS as measured by an adherence score, is associated with reduced mortality.
Significance

• This study will determine the impact of a PARDS MV bundle on mortality and other clinical outcomes (RESEARCH)

• This study will improve adherence to PARDS MV guidelines advocated by international authorities (QUALITY)

• This study will standardize MV practices in PARDS laying the foundation for more comparable trials in the future (FUTURE RESEARCH)
Methodology

• Multi-center, before-and-after comparison study

• Recruitment of patients with PARDS will be based on the PALICC definition

• Recruitment period approximately 4 years:
  • Baseline (control) data can be collected retrospectively/prospectively in the 2-year period prior to bundle implementation
  • Bundle implementation with 1-month wash in period
  • Prospective data collection for the next 2 years post-implementation
Methodology

• Seek approval by PICU medical and nursing stakeholders

• Championed by intensivist and respiratory therapist/nurse

• Training/ education sessions for all PICU staff

• Posters and reminders in the unit and at patient bedside

• Regular updates at administrative meetings
LPMV team

• Medical
  - Site-PI
  - Team member

• Respiratory Therapist representative (optional)
  - Team member
  - Team member

• Nursing representative
  - Team member
  - Team member
Screening

**PARDS Screening Process**
- Screen all patients daily at 8am and 2pm

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**Patient on NIV or Invasive Mech Vent**
- Yes
  - For patients on NIV, calculate SF or PF
  - For patients on invasive mechanical ventilation, calculate OI or OSI.

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**SF < 264 / PF < 300**
- Yes
- Absence of Perinatal Lung Disease
  - Yes
  - End of Screening. Exclude Patient.
  - No
  - Continue to monitor patients' SF/PF or OI/OSI daily at 8am and 2pm
- No
  - End of Screening. Exclude Patient.

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**Known insult within 7 days**
- Yes
- Non-cardiac origin of edema
  - Yes
  - New infiltrates on chest x-ray
    - Yes
      - Include Patient.
    - No
      - End of Screening. Exclude Patient.
  - No
    - End of Screening. Exclude Patient.
- No
  - End of Screening. Exclude Patient.
LPMV targets

<table>
<thead>
<tr>
<th>Ventilation</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tidal volume</strong></td>
<td>All patients</td>
</tr>
<tr>
<td>All patients</td>
<td>3-6ml/kg predicted body weight</td>
</tr>
<tr>
<td><strong>Peak/ plateau pressure</strong></td>
<td>All patients</td>
</tr>
<tr>
<td>All patients</td>
<td>Max 29-30cm H₂O</td>
</tr>
<tr>
<td><strong>Permissive hypercapnia</strong></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>pH 7.20-7.30*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygenation</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permissive hypoxia</strong></td>
<td>Mild PARDS</td>
</tr>
<tr>
<td></td>
<td>SpO₂ 92-97%</td>
</tr>
<tr>
<td></td>
<td>Moderate/severe PARDS</td>
</tr>
<tr>
<td></td>
<td>SpO₂ 88-92%*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive end expiratory pressure</th>
<th>Incremental FiO2/PEEP combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FiO₂</strong></td>
<td>.30</td>
</tr>
<tr>
<td>PEEP</td>
<td>5-7</td>
</tr>
<tr>
<td>FiO₂</td>
<td>.70</td>
</tr>
<tr>
<td>PEEP</td>
<td>12</td>
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</tbody>
</table>
Preliminary Data from KKH

• Lung Protective Mechanical Ventilation Strategies in Pediatric Acute Respiratory Distress Syndrome; single centre (completed)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (N = 132)</th>
<th>No LPMV (N=69)</th>
<th>LPMV (N=51)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>28 (21.2)</td>
<td>18 (26.1)</td>
<td>10 (15.9)</td>
<td>0.152</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>17.5 (0.0, 23.0)</td>
<td>19.0 (0.0, 23.0)</td>
<td>16.0 (2.0, 23.0)</td>
<td>0.697</td>
</tr>
<tr>
<td>PICU-free days</td>
<td>14.0 (0.0, 21.0)</td>
<td>16.0 (0.0, 22.0)</td>
<td>13.0 (0.0, 21.0)</td>
<td>0.233</td>
</tr>
</tbody>
</table>
Preliminary Data – PACC MAN collaboration

• Risk Stratification in Pediatric Acute Respiratory Distress Syndrome: A Multicenter Observational Study (completed)

• Study design: Retrospective multicenter (n=10 sites)
• Patients: PARD S
• Intervention: NA
• Outcome: Mortality

Demonstrated variability in management and outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (n=373)</th>
<th>Mild (n=89)</th>
<th>Moderate (n=149)</th>
<th>Severe (n=135)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator free days</td>
<td>16 (0, 23)</td>
<td>22 (17, 25)</td>
<td>16 (0, 23)</td>
<td>6 (0, 19)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of MV</td>
<td>9 (4, 16)</td>
<td>6 (3, 9)</td>
<td>10 (5, 16)</td>
<td>11 (5, 21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PICU free days</td>
<td>14 (0, 22)</td>
<td>19 (11, 24)</td>
<td>15 (0, 22)</td>
<td>5 (0, 20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of PICU stay</td>
<td>11 (6, 22)</td>
<td>9 (5, 16)</td>
<td>12 (7, 24)</td>
<td>13 (6, 25)</td>
<td>0.010</td>
</tr>
<tr>
<td>PICU mortality</td>
<td>113 (30.3)</td>
<td>11 (12.4)</td>
<td>046 (30.9)</td>
<td>056 (41.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>100-day mortality</td>
<td>126 (39.7)</td>
<td>14 (18.7)</td>
<td>50 (39.1)</td>
<td>62 (54.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
PARDSProAsia study

Phase I (in progress)
- Study design: Prospective observational multicenter (n=16 sites)
- Patients: PARDS
- Intervention: NA (standard care)
- Outcome: Mortality
- Aims:
  - Establish reliable screening process for 100% identification
  - Determine recruitment rate
  - Establish feasibility of data collection tool
  - Confirm baseline ventilation management

Phase II (current proposal)
- Study design: Before-after comparison design
- Patients: PARDS
- Intervention: LPMV bundle
- Outcome: Mortality
- Aims:
  - Hypothesis testing
Potential Challenges

• Adherence to protocol elements in the pre-bundle arm?
  • If this is high, comparison will be difficult

• Data Quality
  • Pre and post data need to be comparable

• Secular Trend
  • The longer the study, the greater the risk of secular trend biasing results
  • Staggering the protocol start time in each center will help

• Large sample size
  • Assuming 1/3 risk reduction (from 25% to 17%), 16 centers with variability in number of subjects and mortality, approximately 500 in each pre/post arm
Funded by Pediatric Academic Clinical Programme Singhealth under grant reference number PAEDSACP-TCL/2020/RES/001