Case 3

The use of proning in the management of Acute Respiratory Distress Syndrome

Clinical Problem

This expanded case summary has been chosen to explore the rationale and evidence behind the use of proning as part of the ventilation strategy in Acute Respiratory Distress Syndrome (ARDS).

A 54 year old woman presented to the Intensive Care Unit (ICU) 12 days after right lower lobectomy for lung cancer. She had a background of chronic kidney disease, hypertension and had previously had a myocardial infarction. The surgery had been undertaken with curative intent. She was admitted for management of type 1 respiratory failure secondary to hospital acquired pneumonia and an acute kidney injury.

She was initially managed conservatively with non-invasive ventilation and fluid resuscitation. She slowly worsened over a period of one week, developing severe ARDS. The decision was made to intubate and ventilate her.

Management

Following her intubation she remained severely hypoxic and difficult to ventilate. In order to maintain an acceptable pO₂ (i.e. 8 kPa) her fractional inspired oxygen (FiO₂) requirements were in excess of 0.65. She deteriorated further overnight and on the following day was requiring an FiO₂ of 0.85. Lung protective ventilator strategies were employed including: 6ml/kg ideal body weight (IBW), tidal volumes, paralysis, increased Positive End Expiratory Pressure (PEEP), inverse inspiratory:expiratory ratios, and permissive hypercapnia. She was referred to Wythenshawe Hospital for consideration of Extra Corporeal Membrane Oxygenation (ECMO), at the time the intention was only to transfer if she deteriorated further. Her AKI also started to worsen.

The decision was made to utilise proning. The tables below show her ventilator settings and blood gases before and a few hours after proning (tables 1 & 2).

<table>
<thead>
<tr>
<th>Ventilator Settings</th>
<th>Before</th>
<th>2 hours after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator Mode</td>
<td>PC</td>
<td>VC+</td>
</tr>
<tr>
<td>Rate</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>I:E</td>
<td>1.5:1</td>
<td>1.5:1</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Peak Pressure (cmH₂O)</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Tidal Volume (ml)</td>
<td>329</td>
<td>343</td>
</tr>
</tbody>
</table>

Table 1 – Ventilator Settings
<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th></th>
<th>After</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.21</td>
<td></td>
<td>7.25</td>
<td></td>
</tr>
<tr>
<td>pCO\textsubscript{2} (kPa)</td>
<td>11.3</td>
<td></td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>pO\textsubscript{2} (kPa)</td>
<td>9.8</td>
<td></td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>BE</td>
<td>5.3</td>
<td></td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 – Arterial Blood Gases

As the values above demonstrate, proning improved the blood gas results in this patient. The improved PaO\textsubscript{2}:FiO\textsubscript{2} ratio (14 to 19) was sustained whilst the patient was prone overnight.

The following day the patient’s AKI had worsened to the point of requiring renal replacement therapy (RRT), which was instituted.

Three periods of approximately 12 hours proned were used. It was halted for several reasons: there was a degree of improvement in both FiO\textsubscript{2} and airway pressures, the third period of proning failed to show an improvement in PaO\textsubscript{2}:FiO\textsubscript{2} ratio and when prone there were access problems with her RRT. She did not suffer any complications of proning beyond the anticipated facial swelling.

At the time of writing the patient remains ventilated on ICU, her oxygenation never deteriorated to the point where ECMO was felt to be indicated. She has been on intensive care for over 30 days. She remains RRT dependent. Her stay has been complicated by systemic candida infection, a cerebrovascular accident and recurrent ventilator associated pneumonias.

**Discussion**

Proning is an adjunct for improving oxygenation and ventilation in ARDS patients, it is used alongside other lung protective strategies. It was first described in 1976\textsuperscript{1}.

The improvements in oxygenation and ventilation are thought to be due to a number of factors\textsuperscript{2}:

- Changes in thoracic and abdominal compliance leading to improved distribution of ventilation
- Improved and sustained recruitment
- Secretion drainage
- More homogenous perfusion
- Reduction in extravascular lung water
- Reduction in ventilator induced lung injury (VILI)

There have been six randomised controlled trials over the last decade studying the use of proning in adults with Acute Lung Injury (ALI, PaO\textsubscript{2}/FiO\textsubscript{2}}
<300 mmHg (40 kPa) and ARDS (PaO\textsubscript{2}/FiO\textsubscript{2} <200 mmHg (26.7 kPa)). Gattinoni and colleagues (The Prone-Supine study group) undertook an international multi-center randomised controlled trial (RCT) with the intention of demonstrating a survival benefit\textsuperscript{3}. This followed trials showing an improvement in oxygenation\textsuperscript{4} and reduced incidence of VILI in animal models\textsuperscript{5}.

The Gattinoni trial recruited patients over the age of 16 with ALI or ARDS. Randomisation and study design was robust but it was underpowered and terminated early (due to increasingly poor recruitment). 304 patients were randomised. The treatment group were intended to be prone for at least 6 hours a day for 10 days. The control group were ventilated in a manner considered best practice at the time, this limits the conclusions that can be extrapolated to modern practice as major changes in ventilator strategies occurred with the ARDS network research\textsuperscript{6} that followed this trial. At least some of patients also appear to have been recruited late, with a pressure sore rate of over 20% at trial entry. Follow up was to 6 months for mortality. No mortality difference was found but as per previous trials there was a significant improvement in PaO\textsubscript{2}/FiO\textsubscript{2} ratio in the prone group. Complication rates were acceptable but included an increased incidence of pressure sores.

Other trials have looked at the benefits of earlier and/or more prolonged proning\textsuperscript{7,8}. Guerin and colleagues followed Gattinoni’s trial with a RCT into the benefits of early proning in ALI and ARDS patients. The treatment group were prone for 8 hours per day and intended to be proned soon after diagnosis. Mancebo and colleagues followed this with a RCT in ARDS patients where the treatment protocol involved 20 hours per day in the prone position and patients were recruited early after diagnosis.

Both trials had control groups receiving ventilation at up to 10ml/kg IBW which contrasts to modern accepted practice. The Mancebo study was also terminated early and underpowered. Neither trial showed a mortality benefit.

Voggenreiter and colleagues\textsuperscript{9} studied the effect of prone ventilation in patients with ALI and ARDS following trauma. No evidence of benefit was shown in this subgroup.

More recently Fernandez\textsuperscript{10} compared modern ARDS ventilation with early and prolonged proning. Unfortunately the study terminated early due to poor recruitment (40 patients successfully followed up compared to an intended 250 based on power calculations). A non significant trend to improved survival was shown.

In order to remedy the perceived weakness of previous trials a further trial was undertaken, the Prone-Supine II trial\textsuperscript{11}. This trial was designed to compare modern ARDSnet ventilation with early (<72 hours from diagnosis) and prolonged (aim of 20 hours per day) proning. Furthermore, due to a possible mortality benefit seen during post hoc analysis of the more severely hypoxaemic patients in previous trials, a priori subgrouping to moderate or severe ARDS was undertaken.
The PSII trial was a multi-center, international RCT, randomisation and design was good. They recruited 344 patients with ARDS. 28 day mortality was the primary endpoint, but follow up to 6 months was planned.

There was no difference in mortality for moderate or severe ARDS but again PaO2:FiO2 ratios were significantly improved in the prone group. Complications occurred in 95% of proned patients (compared to 74% of supine). Significant increases in sedative, relaxant and vasopressor requirements were seen. The incidence of loss of vascular access (16% of prone patients) and endotracheal tube displacement (10%) was also significantly increased.

A meta-analysis of the trials by Abroug\textsuperscript{12} reports a reduction in mortality for ARDS patients (excluding those that only meet ALI criteria) that reaches statistical significance (Odds Ratio 0.71, 95% confidence interval = 0.5 to 0.99, P = 0.048). The rigour of this paper can however be questioned as they have included, as an RCT, a trial of poor quality that was not actually randomised\textsuperscript{13}. The inclusion of this paper has generated a statistically significant result, without it significance is not reached (OR 0.73, 95% CI 0.52-1.04). More positively it should be noted that there was no difference shown between prone and supine groups for major airway complications.

The results of meta-analysis must be approached with caution, even when well conducted. Even with analysis of heterogeneity and careful methodology the outcome must be considered potentially erroneous.

**Lessons learnt**

Prior to treating this patient I had not been involved in proning a patient on ICU for several years. It had been my perception that it was now not considered to be a procedure with clinical benefit.

When our patient was proned there was still potential for increasing her FiO\textsubscript{2} and we had therefore not reached a point where there were no other options. There was, however, a clear improvement in blood gas results and a reduction in the FiO\textsubscript{2} which may be beneficial for long term pulmonary function outcome.

The most recent, high quality, trial\textsuperscript{11} failed to demonstrate a survival improvement. I view the results of the meta-analysis as potentially flawed. As such I do not feel there is clear evidence of benefit from this technique. There is however a trend to mortality improvement in ARDS patients and consistent evidence of improvement in PaO2:FiO2 ratios. I am aware that conducting high quality large RCT’s in intensive care is very difficult. As such the possibility of a benefit in severe ARDS can not be dismissed.

The complication rate is alarmingly high in several studies and this must also be considered in the assessment of risk and benefit. Proning clearly needs to
be undertaken with great care, this has significant implications for staffing numbers and time.

Following this review of the evidence I will in future consider the use of proning in patients with severe hypoxia where benefit may outweigh risk. I remain uncertain that a benefit exists but a trend to improvement in mortality has been shown. I do, however, think it may only be safe in large units familiar with the technique. Further RCT’s and more rigorous meta-analysis may clarify the situation.

References
