Does proning patients with refractory hypoxaemia improve mortality?

Clinical problem and domain

I selected this case because although this was the second patient we had proned in our unit within a week, I had not seen a patient proned for hypoxaemia for a few years and was interested to find out whether the evidence shows an improvement in mortality or simply an improvement in arterial blood gas values.

A morbidly obese 43 year-old woman with a history of depression was admitted to the Acute Medical Unit with increasing shortness of breath, a cough with purulent sputum and pleuritic chest pain preceded by a 3 day history of 'flu-like symptoms. She was commenced on intravenous co-amoxiclav and clarithromycin for severe community-acquired pneumonia and was initially managed with oxygen via face mask on the medical ward. She had blood and sputum cultures and an atypical pneumonia screen sent. She began to desaturate over the next few hours and was transferred to the medical high dependency unit (HDU) for oxygen via high flow nasal cannula.

She was reviewed by the Intensive Care team due to her increasing oxygen requirements. On their arrival, she had a respiratory rate of 40/min. Her SpO_2 was 80-85% on FiO_2 1.0, with a pH of 7.39, PaO_2 of 6.9kPa and $PaCO_2$ of 5 kPa. She was haemodynamically stable with a heart rate of 98/min, blood pressure of 150/77mmHg, and warm peripheries. She was pyrexial (tympanic temperature 39ºC). She was intubated in medical HDU and transferred to the Intensive Care Unit (ICU) for ongoing management.

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Management

Her SpO_2 improved marginally to 85-88% following intubation. She was commenced on airway pressure release ventilation (APRV) on arrival in ICU. She continued to have worsening oxygenation and ongoing pyrexia over the next 24 hours and by day 2 in ICU had a PaO_2 of 7.2kPa and $PaCO_2$ of 9.9kPa on FiO_2 0.95 via APRV (P_{high} 30). She had also developed a new wheeze. Transthoracic echocardiogram showed mild left ventricular systolic dysfunction. She was discovered to be positive for Influenza A.

She was referred to the national extracorporeal membrane oxygenation (ECMO) centre, who advised that she would be a candidate for EMCO and suggested a trial of prone ventilation for 16-18 hours. Her sedation was increased and she was commenced on an atracutrium infusion. She was turned prone uneventfully. Her oxygenation gradually improved over the next 6 hours (PaO_2 10.4kPa and $PaCO_2$ 7.5kPa on FiO_2 0.8). Concerningly, by day 3, her procalcitonin increased significantly and she was changed from co-amoxiclav to ceftriaxone in an attempt to increase her *Staphylococcus* and resistant *Haemophilus Influenzae* cover.

She was discussed again with the national ECMO centre. The team from our nearest ECMO centre came to retrieve her, with the initial plan to transfer her on conventional ventilation to their centre. However, she desaturated on moving her on to the transfer trolley with worsening oxygenation despite FiO_2 1.0 and so was commenced on ECMO in

our hospital, transferred uneventfully to the ECMO centre, and began to improve. Unfortunately she subsequently deteriorated, requiring insertion of a second ECMO cannula. Her progress was complicated by a catastrophic intracerebral haemorrhage. Following confirmation of brainstem death and discussion with her family, her organs were retrieved for organ donation.

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Discussion

For many years, prone positioning has been known to improve oxygenation in patients requiring mechanical ventilation.[1,2] Proposed mechanisms for this include an improvement in regional ventilation, increase in lung volume, promotion of alveolar recruitment, and greater uniformity of ventilation/perfusion ratios.[3] It may also prevent ventilator-induced lung injury, by homogenising the distribution of severe stress within the lungs. However, until recently it has not been shown to improve outcome.[4,5]

Unlike ECMO and high-frequency-oscillatory ventilation (HFOV), prone positioning is simple and can be used in any ICU. However it is not without risk. Prone ventilation may worsen chest wall compliance, resulting in an increase in ventilatory pressure and reduction in the tidal volume delivered.[6] There is an increased requirement for sedation and paralysis in prone patients and a significant incidence of airway and facial oedema. Prone ventilation is associated with significant risks, including endotracheal tube displacement or obstruction, venous access displacement and pressure ulcers.[7] Significantly raised intracranial pressure and unstable vertebral fractures are considered absolute contraindications to prone positioning. Therefore experienced staff are required to safely care for prone patients, and particular care should be taken in patients with cardiovascular instability, facial and eye injuries, and recent sternotomy or abdominal incisions.[6]

In their randomised controlled trial (RCT) Gattinoni *et al* randomised patients with acute respiratory failure to receive prone ventilation for 6 or more hours daily or supine ventilation for 10 days. They found no significant difference in mortality or rate of complications between the two groups.[4] Similarly, Guérin *et al* (2004) did not find a difference in 28 or 90-day mortality between the prone and supine groups in their RCT. One reason for this may be the lack of a predetermined ventilation algorithm. Ventilation was adjusted at the discretion of each centre. They also noted that patients in the prone group had a significantly greater PaO_2: FiO_2 ratio, lower incidence of ventilator-associated pneumonia (VAP), and greater incidence of pressure sores and endotracheal tube obstruction.[4]

Findings from the five main studies looking at whether prone positioning is associated with improved mortality are summarised in Table 1, listed from left-to-right in chronological order. Of note, only the two most recent (Taccone[8] and Guérin 2013[9]) used lung-protective ventilation. The first three (Gattinoni[4], Guérin 2004[5], Mancebo[10]) allowed crossover from one arm of the study into the other, whereas in the two most recent studies, a patient in the supine arm of the study could only be turned prone as a rescue therapy. The first two studies had an average prone position session of 7 or 8 hours. These methodological differences may explain why a mortality benefit with prone positioning has not been demonstrated until recently.[7]

	First author [ref.]		First author [ref.]		
	Gattinoni [ref.]	Guérin [ref.]	Mancebo [ref.]	Taccone [ref.]	Guérin [ref.]
Patients n					
Supine position	152	378	60	174	229
Prone position	152	413	76	168	237
Patients with ARDS %					
Supine position	93.3	28	100	100	100
Prone position	94.7	33.9	100	100	100
Pa_{O_2}/Fi_{O_2} at inclusion mmHg	127	150	147	113	100
Tidal volume at inclusion mL·kg^{-1}	10.3 MBW	8 MBW	8.4 PBW	8 PBW	6.1 PBW
PEEP at inclusion cmH_2O	10	8	12	10	10
Prone position session duration[#] h	7	8	17	18	17
Mortality %					
Supine position	25	31.5	58	32.8	32.8
Prone position	21.1	32.4	43	31	16

ARDS: acute respiratory distress syndrome; Pa_{O_2}: arterial oxygen tension; Fi_{O_2}: inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; MBW: measured body weight; PBW: predicted body weight. #: average hours per session.

Table 1: Results from the 5 main studies into mortality benefit from prone ventilation. From Guérin, 2014.

The Prone-Supine II study, conducted by Taccone *et al*, was a multi centre unblinded RCT. They randomised patients with severe acute respiratory distress syndrome (ARDS) to either supine position or prone position (aiming for 20 hours per day). They reported no significant survival benefit with prone positioning. They found a significant increase in complications in the prone group, including airway obstruction, transient desaturation, cardiovascular instability, loss of venous access, and vomiting.[8]

The 2013 Proning Severe ARDS Patients (PROSEVA) trial was a multicentre prospective RCT investigating the effect of early prone positioning on the outcomes of patients with severe ARDS. Their definition of severe ARDS was patients receiving mechanical ventilation with at least 5cm of water positive end-expiratory pressure (PEEP), fraction of inspired oxygen of ≥0.6, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2 :FiO_2 ratio) of less than 150mmHg, and a tidal volume of approximately 6ml/kg predicted body weight.[9] Of note, their definition of severe ARDS differs from the commonly accepted Berlin criteria, as it was conducted prior to publication of these.

The PROSEVA group randomised 466 patients with severe ARDS to either at least 16 hours in the prone position or remaining supine. They reported that the 28-day mortality in the prone group (16%) was significantly less than that in the supine group (32.8%). Ninety-day mortality was also significantly lower in the prone group (23.6%) than in the supine group (41%). They noted no significant difference in complications between the 2 groups, apart from a higher incidence of cardiac arrests in the supine group.[9] This may be relevant, however, as the increased mortality in supine patients may be because more of them had suffered a cardiac arrest, rather than because they were supine. One of the reasons cited by the authors for the lack of increase in complications in the prone group is that the ICUs involved were all highly experienced at positioning patients prone. There were some differences between the groups, including baseline Sequential Organ Failure Assessment (SOFA) score, vasopressor use and the use of neuromuscular blockers. This may have affected the results. The PROSEVA trial involved a highly-selected population, and had several non-inclusion criteria. This suggests that their findings of a mortality benefit may require selection of appropriate patients.

In their 2008 meta-analysis, Abroug *et al* did not find a significant effect of prone positioning on mortality in patients with ARDS or acute lung injury (ALI).[1] Prone positioning

did increase the PaO_2: FiO_2 ratio and reduce the rate of VAP (although this was not statistically significant). They found no difference in complication rates between prone and supine positioning. Studies on this topic are difficult to compare due to significant heterogeneity, such as inclusion of patients of varying severities of ARDS and variations in intensity of prone positioning.

Sud *et al* conducted a meta-analysis in 2010, and reported that prone positioning reduced mortality in severe hypoxaemia (PaO_2: FiO_2 ratio of ≤ 100mmHg) but not in less severe cases. They also found an increase in the PaO_2: FiO_2 ratio and a lower incidence of VAP in prone patients, however noted a significant increase in the incidence of endotracheal tube obstruction and pressure sores.[2] They found an improvement in mortality with longer durations of prone positioning, however pointed out that these studies also used lung-protective ventilation not used in the earlier studies.

The findings by Sud *et al* were confirmed by Hu *et al* in their 2014 meta-analysis. Their definition of severe ARDS was a PaO_2 :FiO_2 ratio of ≤ 100mmHg. They reported that prone positioning significantly reduced the 28-30 mortality, with a relative risk of 0.71. Prone positioning with a PEEP ≥ 10cmH_2O also reduced 60 and 90-day mortalities, with relative risks of 0.82 and 0.57 respectively.[3] It is not clear whether the benefit of high PEEP suggests a synergistic effect with prone positioning, or whether it is simply a marker or disease severity. When studies were stratified according to duration in the prone position, a significant reduction in 28-30 day mortality was seen in patients who were in the prone position for more than 12 hours per day, but not in those who were prone for less than or equal to 12 hours per day. It is not clear from their meta-analysis if more time in the prone position correlates with a further improvement in mortality or what the threshold is at which a mortality benefit is seen. They concluded that prone positioning reduces the mortality of severe but not mild-moderate ARDS.[3]

Most of the current literature on prone ventilation focuses on ARDS. Although it is likely that prone ventilation also aids with hypoxia from other causes, there is a danger in extrapolation findings from these studies to other pathologies which the studies did not investigate.

1274 words

Lessons learnt

I have learned that as well as increasing oxygenation, prone positioning does improve mortality in severe ARDS when compared to supine positioning, when used early and in relatively long sessions. However, PROSEVA may over-estimate its effect and under-estimate complication rates due to use of very experienced staff and a highly selected population. I believe it does have a role in the general ICU, but requires appropriate training and staffing. The optimal duration of prone positioning is not yet known.

79 words

Total 1890 words

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