Prone position and pressure control inverse ratio ventilation in H1N1 patients with severe acute respiratory distress syndrome

Pradeep M. Venkategowda, S. Manimala Rao, Yogesh R. Harde, Mithilesh K. Raut, Dnyaneshwar P. Mutkule, Kartik Munta, Mallela V. Rao

Introduction

Acute respiratory distress syndrome (ARDS) is a complex syndrome with varied etiology. Influenza viral infection causing severe ARDS is one of the leading causes of increased mortality in the recent years. First case of H1N1 infection was reported by central of disease control in California – April 2009[1] and in India it was reported in Hyderabad - May 2009.[2] Most patients who die due to influenza infection are because of severe hypoxia and multi-organ dysfunction syndrome (MODS).

In 2009 influenza pandemic, there was high mortality in patients with severe ARDS even though patients were ventilated with low tidal volume (volume control) ventilation. Multiple ventilation strategies and rescue therapies have been used to improve oxygenation. Low tidal volume ventilation (volume control) with prone position – PROSEVA trial has shown good outcome.

Abstract

**Aim:** To observe the 28 and 90 days mortality associated with prone position and assist control-pressure control (with inverse ratio) ventilation (ACPC-IRV).

**Materials and Methods:** All patients who were admitted to our medical Intensive Care Unit (ICU) who are positive for H1N1 viral infection with severe acute respiratory distress syndrome (ARDS) and requiring invasive mechanical ventilation in prone position were included in our prospective observational study. Six patients who are positive for H1N1 required invasive ventilation in prone position. These patients were planned to ventilate in prone for 16 h and in supine for 8 h daily until P/F ratio >150 with FiO2 of 0.6 or less and positive end-expiratory pressure <10 cm of H2O. **Results:** At admission, among these six patients the mean tidal volume generated was about 376.6 ml which was in the range of 6–8 ml/kg predicted body weight. The mean lung injury score was 3.79, mean PaO2/FiO2 ratio was 52.66 and mean oxygenation index was 29.83. The mean duration of ventilation was 9.4 days (225.6 h). The ICU length of stay was 11.16 days. There was no mortality at 28 and 90 days. **Conclusion:** Early prone combined with ACPC-IRV in H1N1 patients having severe ARDS can be used as a rescue therapy and it should be confirmed by large observational studies.

**Keywords:** Influenza A virus, inverse ratio ventilation, pressure control ventilation, prone position, severe acute respiratory distress syndrome

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as compared to low tidal volume ventilation (volume control) with supine position.\textsuperscript{[3]}

In our institution we commonly practice assist control-pressure control with inverse ratio ventilation (ACPC-IRV) for ventilating severe ARDS patients. In our study we combined this ventilation strategy along with prone positioning as a rescue therapy, when the normal supine position and ACPC-IRV failed to improve oxygenation after 12 h of initiation of ventilation.

Materials and Methods

During study period between June 2014 and February 2015, 43 patients were positive for nasopharyngeal or throat swab reverse transcriptase - polymerase chain reaction\textsuperscript{[4]} for H1N1 and only 17 patient’s required invasive ventilatory support (ACPC-IRV).

Out of 17 patients, 11 patients showed improvement in terms of oxygenation with regular supine ventilation at the end of 12 h (that is requiring FiO\textsubscript{2} < 0.6 or less, P/F ratio > 150 and positive end-expiratory pressure (PEEP) <10 cm of H\textsubscript{2}O) and hence continued the same supine ventilation. Table 1 showing the P/F ratio and Intensive Care Unit (ICU) length of stay between prone and supine ventilated patients.

Six patients didn’t show any improvement after 12 h from the commencement of invasive ventilation in supine and hence they were considered for either prone ventilation/extracorporeal membrane oxygenation (ECMO) as salvageable therapy.

Prone ventilation or ECMO therapy consent was initiated between 12 and 36 h of admission to medical ICU for those six patients who didn’t improve with normal pressure control with inverse ratio and supine ventilation (1:1 ratio). All six patient attendees agreed for prone ventilation as a salvage therapy and also ethics committee clearance was taken. These patients were planned to prone for 16 h and supine ventilation for 8 h daily till patient is able to maintain a P/F ratio >150 with FiO\textsubscript{2} of 0.6 or less and PEEP <10 cm of H\textsubscript{2}O. We followed these six patients who underwent prone ventilation till their hospital stay and followed later up to 90 days.

Results

Table 2 shows the demographic data of these six patients. Among these patients, there were four males and two females. The mean age was 46.16 years. Two patients did not had any co morbidities, where as three patients had only hypertension and remaining one patient had diabetes and hypothyroidism along with hypertension. The mean duration of fever to hospital admission was 6 days.

All these six patients had fever, cough and dyspnoea where as generalized weakness, nausea, vomiting and mean arterial pressure (MAP) <65 mmHg were seen in four patients. Other less common clinical features are headache, bradycardia, pleuritic chest pain and diarrhoea. The mean hemoglobin was 10.93 g/dl and total leucocyte count – 5350 cells/cumm. The serum electrolytes, liver function tests and renal function tests, prothrombin time, International Normalized Ratio and activated partial thromboplastin time were in normal range.

The ventilator setting at the initiation of ventilation has been showed in Table 3. All six patients were intubated and connected to the ACPC-IRV. The mean tidal volume generated was about 376.6 ml which was in the range of 6–8 ml/kg predicted body weight at the beginning.

| Table 1: The PaO\textsubscript{2}/FiO\textsubscript{2} ratio and Intensive Care Unit length of stay between prone and supine ventilated patients |
|---------------------------------|------------------|------------------|
| Patients who did not improve with initial supine ventilation and later ventilated in prone position | Patients who showed improvement with initial supine ventilation and later continued only in supine position |
| Number of cases | 6/17 | 11/17 |
| PaO\textsubscript{2}/FiO\textsubscript{2} ratio | 52.66 | 112.24 |
| Number of ventilator days | 9.4 | 5.2 |
| ICU length of stay (days) | 11.16 | 7.4 |

Table 2: Demographic profile of 6 prone ventilated patients

<table>
<thead>
<tr>
<th>Profile</th>
<th>Mean (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.16</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>2</td>
</tr>
<tr>
<td>Males</td>
<td>4</td>
</tr>
<tr>
<td>Duration from onset of fever to hospital admission</td>
<td>6 days (mean)</td>
</tr>
</tbody>
</table>

Table 3: Ventilator settings of 6 prone ventilated patients at admission

<table>
<thead>
<tr>
<th>Profile</th>
<th>Mean (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of ventilation</td>
<td>Assist control/pressure control (inverse ratio ventilation)</td>
</tr>
<tr>
<td>Average tidal volume</td>
<td>376.66 ml</td>
</tr>
<tr>
<td>Frequency</td>
<td>31 breaths/min</td>
</tr>
<tr>
<td>FiO\textsubscript{2}</td>
<td>0.96</td>
</tr>
<tr>
<td>PEEP</td>
<td>14</td>
</tr>
<tr>
<td>Pi</td>
<td>20.66</td>
</tr>
<tr>
<td>I: E ratio</td>
<td>1:1-2:1</td>
</tr>
</tbody>
</table>

I: E: Inspiratory: expiratory; Pi: Inspiratory pressure; PEEP: Positive end-expiratory pressure
The Inspiratory: Expiratory (I: E) ratio was initially kept 1:1 and later modified according to the PaO\textsubscript{2} values (maximum was 2:1). The mean inspiratory pressure (Pi) was 20.66 cm H\textsubscript{2}O, which was kept to achieve a tidal volume of 6–8 ml/kg predicted body weight and later reduced to about 6 ml/kg predicted body weight. The PEEP of 14 cm H\textsubscript{2}O was kept initially and later reduced based on oxygenation parameter (never used more than 14 PEEP). The mean frequency and fraction of inspired oxygen were 31 breaths/min and 0.96 respectively. Figure 1 showing patient being ventilated in prone position.

Table 4 shows the oxygenation parameters at admission. The mean lung injury score (LIS) was 3.79, mean PaO\textsubscript{2} / FiO\textsubscript{2} ratio was 52.66 and mean oxygenation index was 29.83. All six patients were proned for 16 h each day. The mean duration from ICU admission to initiation of prone ventilation was 30.66 h. The mean duration of ventilation was 9.4 days (225.6 h). The mean duration of prone and supine ventilation was 66.66 and 159.6 h respectively. The ICU length of stay was 11.16 days. There was no mortality at 28 and 90 days.

The management and complications have been shown in Table 5. Capsule oseltamivir 150 mg twice daily was used for 10 days in view of severe infection. We used tablet prednisolone 40 mg twice daily for 5 days. Patients were sedated and paralyzed using midazolam and atracurium for 2 days and later tapered slowly (average duration of 4.16 days). Vitamin-C (10 days) and omega-3 fatty acids (3 days) were also used in all six patients. Four patients required noradrenalin infusion and one patient vasopressin infusion to maintain MAP > 65 mmHg. Two patients had severe left ventricular dysfunction (myocarditis) and managed with dobutamine infusion.

Orciprenalin was used in two patients for 7 days (10 mg thrice daily) in view of bradycardia. Due to prolonged ventilation required in two patients, they were tracheostomised and later successfully decannulated. With regards to complication, ventilator associated pneumonia was seen in two patients, acute kidney injury in two patients, myocarditis in two patients, critical illness myopathy and atrial fibrillation in one patient each. None of our patients had pneumothorax.

**Discussion**

Low tidal volume ventilation (ARDS network trial) has shown better outcome in patients having severe ARDS.\cite{5} There is still confusion regarding which rescue mode is best among available treatment. Recently prone position and low tidal volume ventilation has shown better mortality benefit as compared to supine position and low tidal volume ventilation. Combination of pressure control and IRV has been used less frequently for severe ARDS ventilation. In our ICU we commonly practice ACPC-IRV for ventilating a patient with severe ARDS. In our study population we used pressure control mode.

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**Table 4: Oxygenation parameters of 6 prone ventilated patients at admission**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung injury score</td>
<td>3.79</td>
</tr>
<tr>
<td>PaO\textsubscript{2} / FiO\textsubscript{2} ratio</td>
<td>52.66</td>
</tr>
<tr>
<td>Oxygenation index</td>
<td>29.83</td>
</tr>
<tr>
<td>hours from ICU admission to initiation of prone ventilation (h)</td>
<td>30.66</td>
</tr>
<tr>
<td>Mean hours of prone/supine ventilation</td>
<td>66.66/159.6</td>
</tr>
<tr>
<td>Number of ventilator days</td>
<td>9.4</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>11.16</td>
</tr>
<tr>
<td>28 and 90 days mortality</td>
<td>0</td>
</tr>
</tbody>
</table>

ICU: Intensive Care Unit

**Table 5: Management and complications occurred during Intensive Care Unit stay**

<table>
<thead>
<tr>
<th>Profile</th>
<th>n=6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>150 mg twice daily for 10 days</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40 mg twice daily for 5 days</td>
</tr>
<tr>
<td>Atracurium + midazolam</td>
<td>Average 4.16 days in tapering dose</td>
</tr>
<tr>
<td>Vitamin-C</td>
<td>500 mg once daily for 10 days</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>100 ml once daily for 3 days</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>4 patients for average 6 days</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>1 patient for 3 days</td>
</tr>
<tr>
<td>Orciprenalin</td>
<td>2 patients for 7 days (10 mg thrice daily)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2 patients for average 4 days</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>2 patients</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
</tr>
<tr>
<td>VAP</td>
<td>2 patients</td>
</tr>
<tr>
<td>AKI</td>
<td>2 patients</td>
</tr>
<tr>
<td>CIM</td>
<td>1 patient</td>
</tr>
<tr>
<td>Pneumo-thorax</td>
<td>0 patients</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>2 patients</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 patient</td>
</tr>
</tbody>
</table>

AKI: Acute kidney injury; VAP: Ventilator associated pneumonia; CIM: Critical illness myopathy
with IRV along with prone positioning [Figure 2] as a rescue therapy in H1N1 patients with severe ARDS who failed the initial ACPC-IRV.

Prone ventilation has been used as one of the rescue therapy in patients having severe hypoxia related to severe ARDS. Recent study by Guérin et al.\(^3\) have shown that prone ventilation in severe ARDS has better outcome compared to supine ventilation with significantly decreased in 28 and 90 day mortality.

The prone position has been used in severe ARDS patients since 1974 for improvement in oxygenation. Maximum improvement has been seen in patient having severe hypoxemia. Multiple mechanisms are involved in improvement of systemic oxygenation during prone ventilation such as, reduction of compression of caudal lung by cardiac and abdominal contents, reinflation of more dorsal lung compared to ventral lung, diaphragm shape, changes in hypoxic pulmonary vasoconstriction and differential production of nitric oxide at different parts of the lung. Prone positioning has shown to cause more homogenous lung inflation with reduction in ventilator induced lung injury. Richter et al.\(^6\) showed that prone or steep lateral decubitus position can decrease intrapulmonary shunt and improve oxygenation.

Prone-supine study-1\(^7\) used 6 h of prone position daily for 10 days showed no difference in terms of mortality and complication as compared to conventional ventilation. Gattinoni et al.\(^8\) showed that during prone ventilation, the reduction in partial pressure of carbon dioxide of 1 mm Hg or more showed increase in survival rate. Prone-supine study-2\(^9\) 20 h of prone ventilation per day also showed similar mortality at 28 days as compared to supine group and more complication in prone group. Systemic review\(^10\) showed no reduction in mortality or duration of ventilation but only improvement in oxygenation. Hence this prone position can be used as rescue strategy to improve oxygenation. A review of all meta analyses\(^11\) showed reduced mortality in patients with severe hypoxemia. Recently PROSEVA trial\(^12\) has shown significant reduction in 28 and 90 days mortality when prolonged prone positioning (16 h of prone per day) in severe ARDS patients as compared to conventional ventilation. In our observational study we also used prone positioning for 16 h per day without any mortality at 28 and 90 days. Six patients didn’t show any improvement with ACPC-IRV and hence they were considered for either prone ventilation or ECMO as salvageable therapy. Figure 1 showing chest X-ray of our first patient with severe ARDS. These patients were planned to prone for 16 h and supine ventilation for 8 h in total 24 h. Only supine ventilation was maintained when patient is able to maintain P/F ratio >150 with FiO\(_2\) of 0.6 or less and PEEP <150 cm H\(_2\)O.

In our study group the mean age was 46.16 years (males-4 and females-2). Hypertension was seen among 4 of 6 patients included in the study. Most common clinical features are fever, cough and dyspnoea followed by generalized weakness, nausea, vomiting, MAP <65 mmHg, headache, bradycardia, pleuritic chest pain and diarrhoea. The mean duration of fever to hospital admission was 6 days.

The ventilator setting has been shown in Table 3. The mean tidal volume generated was about 376.6 ml which was in the range of 6-8 ml/kg predicted body weight. The I: E ratio was initially kept 1:1 and to a maximum of 2:1. The mean Pi was 20.66 cm H\(_2\)O. The maximum PEEP of 14 cm H\(_2\)O was kept initially and later reduced based on oxygenation parameter. The mean frequency and fraction of inspired oxygen were 31 breaths/min and 0.96 respectively.

The severity of ARDS and duration of ventilation is shown in Table 4. The mean LIS was 3.79, PaO\(_2\)/FiO\(_2\) ratio: 52.66 and mean oxygenation index: 29.83. The mean duration from ICU admission to initiation of prone ventilation was 30.66 h. The mean duration of ventilation was 9.4 days (225.6 h). The mean duration of prone and supine ventilation was 66.66 and 159.6 h respectively.

All six patients were treated with capsule oseltamivir 150 mg twice daily for 10 days since our patients had severe infection with MODS, we used the double dose as recommended by WHO. Tablet prednisolone 40 mg
twice daily for 5 days was used. The role of steroids in management of H1N1 related ARDS is controversial. Few studies\cite{12,13} suggest that early and low dose corticosteroids are inefficient and may be even harmful where as others\cite{14,15} have shown the improvement in LIS and hemodynamic stability. Broad spectrum antibiotics (deescalated later after bronchoalveolar lavage fluid culture and sensitivity) along with Vitamin-C (10 days) and omega-3 fatty acids (3 days) were also used during management of these patients. All patients were sedated and paralysed using midazolam and atracurium for 2 days and later tapered slowly (average duration of 4.16 days). Four patients required noradrenalin infusion and one patient vasopressin infusion to maintain MAP > 65 mmHg. Two patients had severe left ventricular dysfunction (myocarditis) and managed with dobutamine infusion. Orciprenalin was used in two patients for 7 days (10 mg thrice daily) in view of bradycardia.

The ICU mortality of H1N1 patients with severe ARDS is about 10–38% and increases up to 58% in patients requiring invasive mechanical ventilation.\cite{16} Sahoo et al.\cite{17} in their study shown that out of seven patients, five patients had MODS. The commonest organ involved was renal. In our study acute kidney injury was seen in two patients but recovered without any need of dialysis. Ventilator associated pneumonia was seen in two patients (acenetobacter was found in both patients), myocarditis in two patients, critical illness myopathy and atrial fibrillation in one patient each. None of our patients had pneumothorax (probably due to maintenance of lower tidal volume and lesser PEEP).

Figure 3 showing chest X-ray of the same patient at the end of prone ventilation on 6th day.

The ICU length of stay depends upon severity of infection, preexisting comorbidities, BMI > 30, co-infection and MODS.\cite{18} The mean ICU length of stay in our patients was 11.16 days. There was no mortality at 28 and 90 days.

**Conclusion**

Early prone combined with ACPC-IRV in H1N1 patients having severe ARDS can be used as a rescue therapy for better outcome and it should be confirmed by large observational studies.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**


