OUTCOME OF VENTILATION IN HYALINE MEMBRANE DISEASE: THE INDIAN EXPERIENCE

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ABSTRACT

OBJECTIVE
To study the short-term outcome of both preterm and term babies requiring assisted ventilation for hyaline membrane disease and report the complications contributing to morbidity and mortality of these patients from a regional medical college with limited resources.

DESIGN
Retrospective file review.

SETTING
Regional Medical College.

PARTICIPANTS
All babies ventilated for HMD over a 6-year period from June 2008 to June 2014.

OUTCOME MEASURES
Outcome of ventilation and factors contributing to mortality.

RESULTS
Out of 100 babies with hyaline membrane disease who were ventilated, 82% survived. Increasing gestational age and birth weight was associated with survival. The commonest complication was shock (77%) and the commonest cause of mortality was septicaemia (77%). Septicaemia, Disseminated Intravascular Coagulation (DIC) and pulmonary haemorrhage were significantly more common complications babies who died (p<0.05). Binary logistic regression analysis showed that DIC (Odds ratio 5.2 [Confidence intervals [C.I.] 1.1-27.1]) and pulmonary haemorrhage (O.R 18 [1.72-45.2]) to be predictors of mortality. The incidence of intraventricular haemorrhage was 1% and that of pneumothorax was 2%. The initial peak inspiratory pressure administered was significantly lower (p=0.033) and maximum peak end expiratory pressure was significantly higher in those who expired (p=0.027).

CONCLUSION
Outcome of ventilation for hyaline membrane disease improves with increasing gestational age and birth weight. The commonest cause of mortality and morbidity were septicaemia and shock respectively.

KEYWORDS
Neonatal Respiratory Distress Syndrome, Mechanical Ventilation.


INTRODUCTION
Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease (HMD) is one of the most common causes of neonatal respiratory failure. According to the National Neonatal Perinatal Database 2003, HMD was found to affect 1.2% of total live births and contributed to 13.5% of total neonatal deaths.[1] Currently recommended treatment modalities for HMD include oxygen therapy, Continuous Positive Airway Pressure (CPAP), surfactant therapy and mechanical ventilation.

Though most babies can be successfully managed with non-invasive therapy like nasal cannula oxygen and CPAP, mechanical ventilation is required for severe RDS. With the establishment of tertiary neonatal units, these treatment modalities are practiced both in the private and government sector in the country. Studies from apex institutes in the country have reported the profile and outcome of babies with hyaline membrane disease needing assisted ventilation.[2-6] There have been no studies from regional medical college. It is in this background that this study was undertaken to analyse the short term outcome of both preterm and term babies requiring assisted ventilation for HMD and report the complications contributing to morbidity and mortality of these patients from a regional medical college with limited resources.

MATERIAL AND METHODS
This is a retrospective study of course and outcome of all babies (Both extramural and intramural) who required mechanical ventilation for HMD between June 2008 and June 2014. Data was obtained by case file review.
The diagnosis of RDS in term/pre-term babies was based on standard definitions. In the pre-term neonate, a diagnosis of HMD/RDS was made when the baby developed increasing respiratory distress with tachypnoea, retractions and grunting.[7] Typical chest X-ray findings of low volume lungs with a diffuse reticulogranular pattern and air bronchogram supported the diagnosis. A diagnosis of RDS in term babies was made if in addition to the above the distress was: (a) Acute in onset; (b) Had a perinatal triggering insult: such as severe perinatally acquired infection, elective caesarean section, severe birth asphyxia, meconium aspiration syndrome; (c) Progressive respiratory distress occurring shortly after birth, characteristic grunting respiration, retractions during inspiration, cyanosis and reduced or absent breathing sounds.[8]

Babies with associated congenital heart disease, hydrops fetalis, surgical problems and those ventilated for less than 4 hours were excluded from the analysis.

For all babies, maternal, perinatal, neonatal details had been recorded. As per unit protocol the babies with RDS were screened for sepsis with blood routine examination, peripheral smear, band cell count estimation, C-reactive protein, blood culture and chest X-ray. Lumbar puncture was performed if sepsis was diagnosed clinically or by laboratory methods.

All babies with RDS were initially managed on oxygen by head box or by nasal cannula. The clinical progression of the respiratory distress was monitored using the Downes score, oxygen saturation and capillary blood gases. If the baby continued to deteriorate on oxygen therapy and Downes score ≥7, decision was taken to administer surfactant. The required dose of surfactant was administered with manual positive pressure ventilation in between aliquots of surfactant for 15 to 30 seconds. (The unit did not have bubble CPAP or high flow oxygen therapy machines during the study period).

Mechanical ventilation was initiated if (a) Respiratory distress persisted as assessed by Downes score ≥7; (b) Baby was apnoeic at birth or apnoeic spells noted post surfactant administration; (c) In preterms less than 34 weeks if oxygen saturation remained <88% and <94% for >34 weeks' gestation, while receiving oxygen therapy; (e) If after surfactant administration poor respiratory effort or fatigability was noted. If the pre-surfactant blood gas pH was <7.25 or Pa CO2 was >65 mmHg or white out lungs was seen on X-ray (severe RDS), mechanical ventilation was continued without attempting extubation after surfactant administration.

During the study period, parents of 12 babies who required ventilation as a treatment modality did not consent for the same because of concerns regarding neurodevelopmental outcome.

The babies were ventilated with Takaoka ventilator (Atlanta and Carmel models). Pressure limited intermittent mandatory ventilation was the initiation mode. The ventilation was weaned based on the clinical condition and capillary blood gases. Babies requiring high mean airway pressures to maintain oxygenation were paralysed with pancuronium or vecuronium. If oxygen requirement of the ventilated baby remained more than 60% at 24 hours after first surfactant administration, a second dose was given. All details regarding ventilation parameters, re-ventilation if any, complications encountered during ventilation such as shock, sepsis, Disseminated Intravascular Coagulation (DIC), pulmonary haemorrhage, Primary Pulmonary Hypertension of Newborn (PPHN), pneumonia, pneumothorax, patent ductus arteriosus, necrotising enterocolitis, their management, outcome and duration of hospital stay were recorded. The parents of babies who left against medical advice or were referred to other hospitals were contacted and their outcome obtained.

Statistical analysis was done using R software.[9] Comparison between all the above variables was done using survival as the grouping variable. Chi-square test was used for categorical variables and ‘t’ test for continuous variables. A logistic regression analysis was done to look at factors that predicted mortality. P value <0.05 was considered significant for all the tests.

RESULTS
There were a total of 2913 admissions to NICU during the study period (June 2008 - June 2014); 419 (14.4%) babies had respiratory distress syndrome, out of which 297 babies were managed with oxygen by nasal cannula or hood, 22 babies with surfactant therapy followed by nasal cannula oxygen and 100 neonates mechanically ventilated.

Out of 100 babies ventilated, 56 were males. An analysis of the mode of delivery showed that of the ventilated babies, 73% were born by caesarean section, 26% by normal delivery and 1% by forceps extraction. A majority of the babies were inborn (76%); 38% of the mothers received antenatal steroids and the complete course was given for 21%. Out of a total of 100 ventilated, the survival rate was 82%. Ninety seven babies (97%) received surfactant. The mean gestational age and birth weight of the survivors were significantly higher in those who survived (p<0.05) (Table 1).

The survival rate increased with gestational age from 11.1% for <28 weeks, 71.4% for 28-30 weeks, 76.5% for 31-32 weeks, 95.2% for 33-34 weeks, 95.5% for 35-36 to 100% for >37 weeks' gestation (Table 2).

The survival rate according to birth weight was 22.2% for <1 kg, 73.3% for 1 to 1.49 kg, 91.3% for 1.5 to 1.99 kg, 95.2% for 2 to 2.49 kg, 100% for >2.5 kg babies (Table 3).

An analysis of the complications encountered in these babies showed that shock was the commonest complication, which occurred in 77 (77%) babies with a survival of 73.8% (Table 4). Other complications were sepsis, Disseminated Intravascular Coagulation (DIC), pulmonary haemorrhage, Persistent Pulmonary Hypertension of Newborn (PPHN), pneumonia, pneumothorax, necrotizing enterocolitis and Intraventricular Haemorrhage (IVH). The incidence of sepsis was 52%, out of which 45% were late onset sepsis; 55% of those with sepsis had maternal risk factors such as prolonged rupture of membranes (>18 hours), untreated urinary tract infection and vaginal candidiasis. Table 4 describes the complication in ventilated babies. Sepsis, DIC and pulmonary haemorrhage were complications significantly more common in babies who died. On applying binary logistic regression analysis, DIC (Odds ratio 5.2 [confidence intervals (CI) 1.1-27.1]) and pulmonary haemorrhage (OR 18 [1.72-45.2]) were found to be independently predictive of mortality. With regards to chronic complications of ventilation, which developed within 28 days post-ventilation,
bronchopulmonary dysplasia developed in one baby (1%). Retinopathy of prematurity developed in 13%.

Fourteen babies (14%) were re-ventilated for the following indications namely, apnoea of prematurity, sepsis, unresolved HMD, laryngeal oedema, pneumonia, pulmonary haemorrhage and pneumothorax. Survival rate of re-ventilated babies was 64%.

The ventilator parameters were analysed. The age at which ventilation was initiated, duration of ventilation, age of extubation, initial and maximum ventilator settings were considered. The initial Peak Inspiratory Pressure (PIP) administered was significantly lower (p=0.033) and maximum Peak End Expiratory Pressure (PEEP) was significantly higher in those who expired (p=0.027) (Table 5).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean in Survivors</th>
<th>Mean in Expired</th>
<th>P value, SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age (weeks)</td>
<td>34.05 (30.65-37.45)</td>
<td>28.83 (25.6-32.03)</td>
<td>0.001, SD=3.4</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>1.95 (1.26-2.6)</td>
<td>1.14 (0.725-1.55)</td>
<td>0.001, SD=1.14</td>
</tr>
</tbody>
</table>

Table 1: Mean Gestational Age and Birth Weight in Relation to Survival

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Total Number</th>
<th>Number Survived (%)</th>
<th>Survivors (Percentage)</th>
<th>Expired (Percentage)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>9</td>
<td>1 (11.1)</td>
<td>60 (73.9)</td>
<td>17 (22.1)</td>
<td>0.065</td>
</tr>
<tr>
<td>28-30</td>
<td>14</td>
<td>10 (71.4)</td>
<td>38 (47.1)</td>
<td>14 (26.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>31-32</td>
<td>17</td>
<td>13 (76.5)</td>
<td>5 (41.7)</td>
<td>7 (58.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>33-34</td>
<td>21</td>
<td>20 (95.2)</td>
<td>21 (91.3)</td>
<td>21 (95.2)</td>
<td>0.632</td>
</tr>
<tr>
<td>35-37</td>
<td>22</td>
<td>21 (95.5)</td>
<td>1 (4.5)</td>
<td>6 (85.5)</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;37</td>
<td>17</td>
<td>17 (100)</td>
<td>1 (100)</td>
<td>1</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 2: Gestational Age Specific Survival

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number with Complication</th>
<th>Survivors (Percentage)</th>
<th>Expired (Percentage)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>77</td>
<td>60 (73.9)</td>
<td>17 (22.1)</td>
<td>0.065</td>
</tr>
<tr>
<td>Sepsis</td>
<td>52</td>
<td>38 (47.1)</td>
<td>14 (26.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>DIC</td>
<td>12</td>
<td>5 (41.7)</td>
<td>7 (58.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>NEC</td>
<td>8</td>
<td>6 (75)</td>
<td>2 (25)</td>
<td>0.632</td>
</tr>
<tr>
<td>Pulmonary Haemorrhage</td>
<td>7</td>
<td>1 (14.3)</td>
<td>6 (85.7)</td>
<td>0.0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>0.072</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>IVH</td>
<td>1</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 3: Birth Weight Specific Survival

<table>
<thead>
<tr>
<th>Ventilatory Parameters</th>
<th>Mean (Survivors) N=82</th>
<th>Mean (Expired) N=18</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial PIP (cm H2O)</td>
<td>22.04±3.1</td>
<td>20.2±3.2</td>
<td>0.033</td>
</tr>
<tr>
<td>Initial PEEP (cm H2O)</td>
<td>4.57±0.619</td>
<td>4.67±0.68</td>
<td>0.56</td>
</tr>
<tr>
<td>Initial FiO2</td>
<td>0.81±0.208</td>
<td>0.861±0.212</td>
<td>0.36</td>
</tr>
<tr>
<td>Initial MAP (cm H2O)</td>
<td>11.06±1.8</td>
<td>10.2±1.07</td>
<td>0.093</td>
</tr>
<tr>
<td>Maximum PIP (cm H2O)</td>
<td>22.8±3.5</td>
<td>22.5±4.3</td>
<td>0.703</td>
</tr>
<tr>
<td>Maximum PEEP (cm H2O)</td>
<td>4.6±0.62</td>
<td>5±0.76</td>
<td>0.027</td>
</tr>
<tr>
<td>Maximum FiO2</td>
<td>0.834±0.26</td>
<td>0.842±0.243</td>
<td>0.91</td>
</tr>
<tr>
<td>Maximum MAP (cm H2O)</td>
<td>11.6±1.9</td>
<td>11.7±2.3</td>
<td>0.86</td>
</tr>
<tr>
<td>Age of ventilation (hours)</td>
<td>9.1±13.2</td>
<td>9.05±14.1</td>
<td>0.429</td>
</tr>
<tr>
<td>Duration of ventilation (hours)</td>
<td>44.6±28.1</td>
<td>54.4±37.4</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Table 4: Complications in Ventilated Babies

Table 5: Comparison of Ventilator Parameters between Survivors and Expired

DISCUSSION
It is a well-known fact that most government medical colleges function in the face of equipment and manpower resource constraints unlike the corporate sector. This is the first study, which reports survival of HMD babies who have received invasive ventilation from a state medical college in India. Our study results with regard to overall survival may have been affected because of few babies less than 28 weeks who required respiratory support were not ventilated as per parental request. This could be a limitation of our study.

In our study, the survival rate was 82%. The survival rate in males was 82.1% and females 81.8%. The survival rate reported is comparable to other studies from India, which have reported a survival rate of 77% to 84%.[3,4,5,10,11] Our finding that babies with increasing gestational age and birth weight have better survival has been universally reported. [12]

Though shock was the commonest complication in our babies, septicaemia was the commonest complication contributing to mortality which is similar to that reported in other Indian studies.[3,4,5,10,11] In addition to maternal and neonatal factors predisposing to sepsis, infrastructure and staff restrictions of our setting could have contributed to the development of sepsis.

The rate of IVH in our babies was 1%, which is less than other studies which have reported rates between 17 to 51%.[3,4,5,10,11] We found a similar finding with respect to air leak, which was 2% as compared to other studies which had reported 7 to 20%.[13,14] The lower incidence of air leak and
IVH could have been possibly because all babies in our series were sedated, paralysed with pancuronium or vecuronium if mean airway pressure was >13 or ventilator synchrony was observed. Further, the blood pressure was monitored and inotropes titrated accordingly.

This could have reduced the rapid and sudden blood pressure fluctuations, which have been associated with the development of IVH.[13,16] The neuromuscular paralysis is known to have added benefit in the prevention of both pneumothorax and IVH.[17] Bronchopulmonary dysplasia is more commonly found in preterms <30 weeks and <1200 grams. There were very few survivors in this group in our study, which could have contributed to a rate of 1% as compared to 10 to 14% in other studies.[3,11] Retinopathy of prematurity developed in 13 babies (13%) of whom 11% required treatment, which is comparable to other studies.[3,18]

Analysis of the ventilator parameters showed that the initial PIP was higher and the maximum PEEP lower in the survivors as compared to the non-survivors. Other studies have demonstrated a higher mean maximum PIP in non-survivors.[19,20] There was no difference in the age of initiation of ventilation or duration of ventilation between the two groups as demonstrated in a previous study.[21]

CONCLUSION
The survival rate in our study was 82%. Survival improved with increasing gestational age and birth weight. Sepsis, DIC and pulmonary haemorrhage were significantly associated with a poor outcome and septicaemia was the commonest cause of mortality. There was a reduced incidence of IVH and pneumothorax.

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REFERENCES