Outcome of neonates requiring assisted ventilation

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Over a two-year period, we studied a total of 100 newborns delivered in our hospital, needing ventilation. The indications for ventilation, complications, outcome, and factors influencing outcome were analyzed. Of the 100 babies, 54 were preterm, 44 term and 2 post-term. Overall survival was 58%. The commonest indication for ventilation was meconium aspiration syndrome in term babies and hyaline membrane disease in preterms. Babies ventilated for pneumonia had the best outcome, while the poorest outcome was in sepsis. Survival increased significantly with increasing birth weight and gestational age. Downes score, Apgar score and pH at birth did not correlate significantly with outcome. The maximum peak inspiratory pressure requirement was significantly higher in the non-survivors. In pneumonia and sepsis, increased FiO2 requirement significantly impaired survival. The commonest complication was shock. Incidence of disseminated intravascular coagulation, pulmonary hemorrhage and pneumothorax was significantly higher in non-survivors; however, none of these factors was independently predictive of mortality.

***Key words:** neonatal ventilation, outcome, predictors of mortality, indications.*

Assisted ventilation has become an indispensable part of neonatal intensive care. This study was done to assess the current status of neonatal ventilation in a tertiary care neonatal unit in India, to identify the common indications for ventilation, study the course during ventilation, analyze the complications that arise, and evaluate the final outcome as measured by survival.

Material and Methods

Jawaharlal Institute of Postgraduate Medical Education and Research is a tertiary care referral center and an institution of national importance in India. After obtaining the approval of our Institute Research and Ethics Committee, this observational study was conducted in the tertiary care neonatal unit of our hospital over a two-year period (October 2007 – August 2009). On the basis of previously reported survival rates of 51% and 58.3%[1,2] in studies on mechanically ventilated neonates reported from India, with a confidence of 95% and allowing for a variation of 10%, the sample size was calculated to be 100. Totally, 454 babies were ventilated during the study period. Each consecutive baby satisfying the inclusion criteria was included in the study, and we stopped once the sample size of 100 was reached. Only inborn babies who had required intermittent positive pressure ventilation were included. Babies with major congenital anomalies and those who expired within the first four hours of life were excluded. After obtaining informed consent from the parents, the details of the mother and the baby, mode of delivery, indication for any intervention made, and immediate postnatal events like Apgar score and resuscitation done, if any, were recorded. All babies were weighed on admission using a digital electronic weighing scale with an accuracy of 10 g. The indications for ventilation varied among cases. Each of these conditions was diagnosed based on the National Neonatal-Perinatal Database (NNPD) criteria[3]. The babies were ventilated using time-cycled pressure-limited continuous flow ventilators. An initial objective assessment of the respiratory distress of every admitted neonate was made using Downes respiratory distress score[4], a clinical scoring system devised by Downes in 1970 primarily to assess and grade the severity of respiratory distress in respiratory distress syndrome (RDS), which was compared and found to correspond to blood gas values

Downes Scoring for Respiratory Distress[4]

Score	0	1	2
Respiratory rate (per min)	<60	60–80	>80 / apneic episode
Cyanosis	None	In room air	In 40% oxygen
Retractions	None	Mild	Moderate–severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry*	Clear	Delayed / decreased	Barely audible

* Air entry represents the quality of inspiratory breath sounds as heard in the midaxillary line.

All babies were treated according to existing standard management protocol, and requisite investigations were done whenever needed. They were started on intravenous fluids, with the amount and composition depending on the weight and postnatal age. Enteral feeds were introduced when appropriate using expressed breast- milk. All ventilated babies were started on antibiotics. Cefotaxime and gentamicin were used as the first-line antibiotics. Antibiotics were changed according to the clinical condition and culture reports. Surfactant (Survanta) of bovine origin was administered to preterms with hyaline membrane disease (HMD) in doses as recommended by the manufacturers.

Statistical analysis was done using SSPS software (Statistical Packages for the Social Sciences) version 17 for Windows (SPSS Inc., Chicago, IL, USA). Chi-square test was used for categorical variables and Student's unpaired t test for continuous variables. $p<0.05$ was considered significant for all the tests. The variables identified as significant by univariate analysis were further analyzed using multivariate logistic regression.

Results

Overall, 58 babies survived while 42 expired. Fifty-five had normal vaginal delivery and the remaining by other means including cesarean section, assisted breech and instrumental delivery. The general profile of the study population and the survival outcome in relation to various parameters are described in Table I. Meconium aspiration syndrome (MAS) was the commonest indication for ventilation in term babies, whereas in preterms it was HMD. The best outcome was observed in neonates ventilated for pneumonia, with a survival rate of 75%, followed by perinatal asphyxia, MAS, apnea of prematurity, and HMD. The worst outcome was seen in babies with sepsis, with a survival rate of only 46.1%. The factors influencing the outcome of ventilation were analyzed. Although females had a better survival compared to males, the difference was not found to be statistically significant ($p=0.179$). The mean gestational age and mean birth weight of babies who survived were significantly higher in comparison to babies who expired. Presence of obstetric complications was not found to have any significant effect on the outcome. Babies who had higher Downes score on admission (≥ 7) had higher mortality than those with lower scores; however, the difference did not reach statistical significance. Downes score on admission, 5 minute Apgar score and pH at birth did not correlate significantly with outcome (Table II).

An analysis of ventilatory requirements revealed that the maximum peak inspiratory pressure (PIP) requirement during the course of ventilation was significantly higher in the non-survivors compared to that of the survivors. Although the non-survivors required higher FiO2 and maximum positive end-expiratory pressure (PEEP) than the survivors, these differences did not reach statistical significance. When maximum ventilatory requirements during the course of ventilation were analyzed in relation to outcome in individual conditions, it was found that increased FiO2 requirement had a significant difference in outcome in cases ventilated for pneumonia ($p=0.007$) and those ventilated for sepsis ($p=0.044$). In babies ventilated for other indications, there was no significant difference (Table III).

Shock, sepsis/pneumonia, disseminated intravascular coagulation (DIC), pulmonary hemorrhage, air leak syndromes, and persistent pulmonary hypertension in newborns (PPHN)

Table I. Percentage Survival in Relation to the Studied Parameters

Survival in relation to:	Number of babies (total n = 100)	Percentage survival
Sex		
Males	51	52%
Females	49	65.3%
Maturity		
Preterm	54	51.9%
Term	44	65.1%
Post-term	2	100%
Birth weight		
< 1 kg	1	0%
1 – 1.499 kg	24	41.6%
1.5 – 1.99 kg	20	55%
2 – 2.499 kg	18	77.7%
> 2.5 kg	37	63.8%
Gestational age (weeks)		
28-30	16	31.25%
31-32	20	55.5 %
33-34	12	40.0%
35-36	6	66.66%
37-41	44	65.1%
>42	2	100%
Downes score at admission		
< 6	88	60.2%
≥ 7	12	45.4%
5 min Apgar		
≤ 6	37	59.4%
≥ 7	63	58%
Indication		
Pneumonia	12	75.0%
Perinatal asphyxia	11	72.7%
MAS	28	60.7%
AOP	10	60.0%
HMD	25	52.0%
Sepsis	13	46.1%
Others	1	0.0%

MAS: Meconium aspiration syndrome. AOP: Apnea of prematurity. HMD: Hyaline membrane disease.

'Others' included a neonate who was the recipient in a case of twin discordance. She had been antenatally diagnosed to have pericardial effusion and cardiomegaly, presented with cardiac failure at birth, and was ventilated for respiratory distress.

were the complications noted to have occurred during the course of ventilation. Of these, shock was the commonest followed by sepsis/ pneumonia. While the presence of shock, ventilator-associated pneumonia (VAP)/sepsis and PPHN did not have a significant bearing on the outcome, DIC, pulmonary hemorrhage and pneumothorax significantly hampered survival (Table IV). On applying multivariate logistic regression, none of the factors identified as significant by univariate analysis was found to be an independent predictor of mortality.

A total of 25 cases had HMD, among whom 23 received surfactant. Both the babies who did not receive surfactant expired, resulting in 100% mortality in that group.

Discussion

Meconium aspiration syndrome (MAS) was the commonest indication for ventilation in our series. It was the third most common cause for ventilation in studies by Riyas et al.[1], Malhotra et al.[5] and Maiya et al.[6] Among the 28 babies who had MAS in our series, 16 also developed hypoxic ischemic encephalopathy (HIE). Late referrals and mothers presenting in the late stages of labor with fetal distress, thereby precluding the use of elective or emergency

Table II. Profile of Survivors and Non-Survivors

Parameter	Mean in survivors (95% CI)	Mean in non-survivors (95% CI)	p-value Student t test, Standard deviation (SD)
Gestational age (wks)	36.07 (35.02–37.12)	34.48 (33.18–35.77)	0.037, SD = 4.08
Birth weight (g)	2265.69 (2082.07-2449.30)	1933.66 (1721–2192)	0.026, SD = 727.1
Downes score at admission	4.38 (3.87-4.89)	4.38 (3.69-5.06)	0.791, SD = 1.74
5 minute Apgar	7.1034 (6.65-7.56)	6.5250 (5.97-7.08)	0.107, SD = 2.01
pH at admission	7.25 (7.23-7.28)	7.22 (7.18-7.26)	0.158, SD = 0.12

cesarean sections, might be conceived as the reason for the greater number of MAS and HIE babies in our series. Preterm-HMD was the commonest indication for ventilation in most studies, including the series by Singh et al.[7], Nangia et al.[8] and Karthikeyan et al.[9] In our study, HMD was the second commonest indication for ventilation followed by sepsis and pneumonia. Asphyxia was the fifth most common indication in our study. The NNPD 2002 places birth asphyxia as the commonest primary cause of neonatal mortality, with an incidence of 28.8% among all intramural deaths[3]. In our study, survival was 58%, which is comparable to that reported from other neonatal intensive care units (NICUs) in the country. Survival outcome in various studies has ranged from 41.2% to 67.9% (9,10). While Malhotra et al.[5] reported a survival of 62%, most other Indian studies had a survival outcome of around 55%[2,7,11]. In the present study, the best outcome was observed in neonates ventilated for pneumonia, with a survival rate of 75%. Babies with pneumonia had better outcome, with survival rates ranging from 66.6% to 100% in other series (2,5-7,11). The next best outcome was for babies with birth asphyxia (72.7%). In the series by Karthikeyan and co workers[9], out of all causes, babies with perinatal asphyxia had the best outcome, with a survival of 79.3%. Less than 50% survival in asphyxiated babies was reported by Mathur et al.[11] and Riyas et al.[1], while 14% survival was observed in the series by Singh et al.[7]

The commonest indication for ventilation in our series, MAS, had the third best outcome, with a survival of 60.7%. MAS had the best outcome in the series by Malhotra et al.[5] and Riyas et al.[1], with 100% and 63.6% survival, respectively. Poorest outcome was seen in the series by Singh et al.[7] and Karthikeyan et al.[9], where all the babies who were ventilated for MAS expired. Babies with apnea of prematurity in our series had a survival rate of only 60%, as many of them succumbed to superimposed infections during ventilation.

Survival of 52% for HMD in the present series is comparable to most other series. However, Singh et al.[7] and Schreiner et al.[12] had reported better survival in HMD in their series. Natural surfactant (bovine origin) was used in our study selectively for infants with established RDS as rescue therapy and in most cases as late rescue. Whilst natural surfactant is associated with a marginally higher risk of intraventricular hemorrhage compared to synthetic surfactant, it better reduces mortality and the incidence of pneumothorax[13]. Compared to selective use in babies with RDS, prophylactic administration of surfactant produces a better reduction in the incidence of RDS, pneumothorax, pulmonary interstitial emphysema and bronchopulmonary dysplasia, and death[14,15]. Because of resource constraints, we were unable to use surfactant prophylactically, which might also explain the higher mortality for HMD in our series compared to western data. Treating expectant mothers antenatally with corticosteroids when a preterm birth is anticipated has been shown to reduce mortality, RDS, intraventricular hemorrhage, necrotizing enterocolitis, need for ventilatory support and intensive care, and infections in the first 48 hours of life[16]. The use of antenatal corticosteroids has been shown to reduce the need for prophylactic and early rescue surfactant[17]. Furthermore, combined use of antenatal steroids and surfactant has been proven to be more beneficial than either therapy alone[18]. In our study, the influence of antenatal steroids plus surfactant versus surfactant alone without antenatal steroids, on the outcome, was examined. Contrary to our expectation, the difference was not statistically significant, probably because of the small number of cases (only 5 babies) who had received both antenatal steroids and surfactant.

Sepsis caused the worst outcome, with only 46.1% survival. Maiya et al.[6] reported 100% survival in sepsis cases while Karthikeyan et al.[9] and Mittal et al.[2] reported 66.6% and 64.9% survival, respectively. Sepsis had a uniformly poor outcome in all other studies[7,11].

Females were found to have better survival (65.3%) than males (52%), but the difference was not statistically significant. A similar trend was observed in the series by Riyas et al.[1] and Lindroth et al.[19]

We found that the mean gestational age of the newborns who survived was significantly higher than that of the non-survivors, which is consistent with the findings of most other authors[8,9,11]. It was observed that increasing birth weight was associated with better survival. This was consistent with the findings of several other authors[1,5-9,11]. Rich et al.[20] in their study on very low birth weight infants found low birth weight as the best predictor of longer duration of ventilatory support.

The Downes score provides an objective way of assessing any improvement or deterioration in the respiratory status of the baby. In regions with limited resources, where objective measurements are not available, this scoring system provides immense advantage over unsystematic clinical evaluation. Downes and co-workers found that, although the initial score did not bear any relation to the outcome, the score at 12-18 hours provided an estimate of the prognosis, with a higher score indicating poorer prognosis[4]. The majority of the neonates in our series were ventilated immediately after respiratory distress was recognized. Thus, we were not able to study the Downes score at 12-18 hours and beyond. Hence, we tried to correlate the initial score at admission with the outcome. The score was higher among non-survivors, but the difference was not statistically significant.

Arafa et al.[21] in their study found a 5 minute Apgar score of <7 to be significantly associated with mortality. In our series, the mean 5 minute Apgar of survivors was 7.1, whereas that of the babies who expired was 6.52, but the difference was not statistically significant. We compared the pH on admission with the outcome in all the ventilated babies, and found that the mean pH of the survivors was slightly higher than that of the non-survivors and also that babies with a pH of >7.3 had a better survival than those with a pH of <7.299, but the difference was not significant. This was similar to the observation by Mathur et al.[22]

Maximum ventilatory requirements during the course of ventilation were analyzed with the outcome as a whole and separately with each individual indication. The mean of the maximum PIP requirement of the non-survivors

Table III. Comparison of Ventilatory Parameters Between Survivors and Non- Survivors

Ventilatory parameter	Mean maximum in survivors (n=58) (95% CI)	Mean maximum in non-survivors (n=42) (95% CI)	p value, Standard deviation (SD)
PIP (maximum)	17.62 (16.78-18.46)	19.03 (17.64-20.41)	0.04, SD = 3.2
FiO2 (maximum)	56.03 (51.73-60.34)	61.38 (56.33-66.42)	0.108 Overall 0.044 in Sepsis 0.007 in Pneumonia, SD = 16.377
PEEP (maximum)	5.53 (5.32-5.75)	5.75 (5.46-6.04)	0.204, SD = 0.821

PIP: Peak inspiratory pressure. PEEP: Positive end-expiratory pressure.

Table IV. Analysis of Survival in Relation to Complications

Complication	No. of babies with the complication	No. of babies with the complication that survived	% survival in babies with the complication	% survival in babies without the complication	p value
Shock	49	28	57.1	60	0.773
Pneumonia/ sepsis	18	8	44.4	61.7	0.192
Pulmonary hemorrhage	7	1	14.3	62	0.012
PPHN	7	2	28.5	60.8	0.094
DIC	6	1	16.6	61.3	0.029
Pneumothorax	5	0	0	61.7	0.002

PPHN: Persistent pulmonary hypertension in newborns. DIC: Disseminated intravascular coagulation.

was significantly higher than that of the survivors. Mathur et al.[22] observed a similar trend in their study, but the difference was not statistically significant. When we compared the maximum FiO2 requirements with the outcome, we found that the non-survivors had actually required a greater mean maximum FiO2 than the survivors, but the difference was not statistically significant. In babies ventilated for pneumonia, a maximal FiO2 requirement of 60-80% was associated with significantly higher mortality compared to those who had required 40-60%. In babies with sepsis, a requirement of 40-60% resulted in significantly higher mortality than FiO2 of 20-40%. Mathur et al.[22] in their series identified an initial FiO2 requirement of more than 60% as a significant independent predictor of mortality.

Pulmonary hemorrhage occurred in 7 babies, among whom only 1 survived, and the difference was statistically significant. Four of the seven were cases of HMD and developed pulmonary hemorrhage following surfactant administration, a recognized complication of surfactant treatment. Six babies in the series by Karthikeyan et al.[9] developed pulmonary hemorrhage, 5 of them following surfactant administration.

Among all complications, the one that had the greatest association with mortality was air leak syndrome. All 5 babies who had air leaks in our series died. In the 1970s, it was a very common complication, occurring in 20% of all cases and 31% of cases with MAS[12]. In our series, the incidence of air leak syndrome was significantly lower compared to most other studies[6-8,10,11] despite the presence of more babies with MAS (who are more prone to air leaks), which can probably be attributed to the judicious use of pressures and early attempts at weaning.

Although our center uses high-frequency ventilation in selected neonates, in this study, we had included only those babies ventilated by conventional modes. Studies have shown that there is no significant difference in outcome between the conventional and high-frequency modes, provided an optional lung volume strategy is used[23,24]. Utilizing noninvasive modes of ventilation like nasal continuous positive airway pressure (CPAP), nasal intermittent positive pressure ventilation (NIPPV) and methods like mandatory minute ventilation have been shown to decrease some of the long-term complications associated with mechanical ventilation as well as the incidence of post-extubation failure[24,25].

In conclusion, our study reaffirmed that increasing gestational age and birth weight are associated with a better outcome. The mean maximum PIP requirement was significantly higher in the non-survivors compared to the survivors. Although the incidence of DIC, pneumothorax and pulmonary hemorrhage was significantly higher in the non-survivors, none of these factors was found to be independently predictive of mortality. Earlier referral of high-risk pregnancies to tertiary care facilities might increase the use of antenatal steroids, enable better planning of deliveries, provide better outcomes in HMD, and reduce the incidence of MAS in developing nations. Better resource availability allowing earlier and prophylactic use of surfactant might have an impact on the outcome of HMD in our region of the world.

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