

Neonatal mechanical ventilation: Indications and outcome

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Abstract

Background and Aims: Decreasing mortality in sick and ventilated neonates is an endeavor of all neonatologists. To reduce the high mortality in this group of neonates, identification of risk factors is important. This study was undertaken to find out the indications of ventilation and complications in ventilated neonates and also study possible predictors of outcome. **Subjects:** Age <1-month; mechanically ventilated; not having suspected metabolic disorders or congenital anomalies; excluding postoperative patients. **Methods:** Neonates consecutively put on mechanical ventilation during the study period (October 2011 to November 2013) enrolled. Primary disease of the neonates along with complications present listed. Clinical and laboratory parameters analyzed to find the predictors of mortality. **Results:** Total 300 neonates were ventilated. 52% were male. Mean age, weight, and gestational age were 21 ± 62 h, 2320 ± 846.2 g, and 35.2 ± 4.9 weeks, respectively. 130 (43%) neonates died. Respiratory distress syndrome (RDS) (31.1%), sepsis (22.7%), and birth asphyxia (18%) were the most common indications for ventilation. Mortality in ventilated patients with sepsis, pneumonia, RDS or birth asphyxia was 64.7%, 60%, 44.6%, and 33.3%, respectively. Weight <2500 g, gestation <34 weeks, initial pH <7.1, presence of sepsis, apnea, shock, pulmonary hemorrhage, hypoglycemia, neutropenia, and thrombocytopenia were significantly associated with mortality ($P < 0.05$). Resuscitation at birth, seizures, intra ventricular hemorrhage, pneumothorax, ventilator-associated pneumonia, PO_2 , or PCO_2 did not have a significant association with mortality. On logistic regression, gestation <34 weeks, initial pH <7.1, pulmonary hemorrhage, or shock were independently significant predictors of mortality. **Conclusions:** Weight <2500 g, gestation <34 weeks, initial arterial pH <7.1, shock, pulmonary hemorrhage, apnea, hypoglycemia, neutropenia, and thrombocytopenia were significant predictors of mortality in ventilated neonates.

Keywords: Complications of ventilation, neonatal mechanical ventilation, predictors of mortality

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Introduction

Advances in perinatal and neonatal care have significantly reduced neonatal morbidity and mortality rates. Outcome in sick infants has improved significantly, mostly due to more effective newborn intensive care and aggressive respiratory and cardiovascular support. It is

the introduction of widespread mechanical ventilation in the neonatal Intensive Care Units (NICU) during 1960s and 1970s^[1] and its judicious use since, which has revolutionized the outcome and survival of sick

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newborns.^[2] A significant proportion of neonates admitted to NICU require mechanical ventilation; and mechanically ventilated neonates have a high fatality. Survival rate in artificially ventilated neonates is reported as 64% by Trotman^[3] and 67.9% by Karthikeyan and Hossain^[4] though survival of such neonates has been higher in developed countries.^[5] This variation in the mortality has been attributed to more biomedical technological advancements in the developed countries. Various studies in developing countries have shown a mortality rate in the range of 40–60%^[6,7] in ventilated babies. Despite the availability of mechanical ventilation, mortality is still high in sick neonates. So to improve the mortality in ventilated neonates, identification of bad prognostic factors, and their remedy becomes mandatory.

The primary aim of the present study was to find the risk factors responsible for poor outcome in ventilated neonates. We studied numerous clinical, biochemical, and hematological parameters in ventilated neonates and tried to relate them to outcome.

Methods

This prospective study was conducted from October 2011 to November 2013 in the NICU of A Tertiary Care Referral Hospital in North India. All neonates (aged 0–28 days) who required ventilation during the study period were eligible for inclusion in the study. Neonates who had congenital anomalies or suspected metabolic disorders or postsurgical babies were excluded from the study; all other ventilated neonates were included. Clearance was taken from the local ethical committee. Whenever a neonate is ventilated, his parents/guardians are informed as a routine in our NICU by the senior resident on duty. Informed consent was obtained at the same time from the parents/caregivers of every included neonate. For each ventilated neonate information, including age, sex, admission, weight (recorded by electronic weighing machine), gestational age (by modified Ballard's scoring), any maternal illness, type of delivery, any resuscitation at the time of birth, neonatal problems, primary diagnosis, hospital stay, and complications were recorded. The indications for initiation of mechanical ventilation were: (i) $\text{PaO}_2 < 50$, (ii) $\text{PaCO}_2 > 60$ mmHg, (iii) intractable or recurrent apnea, (v) gasping or poor respiration, (vi) O_2 saturation $< 85\%$ on supplemental oxygen, (vii) continuous positive airway pressure (CPAP) failure, defined as worsening respiratory distress, and/or hypoxemia ($\text{PaO}_2 < 50$ mmHg)/hypercarbia ($\text{PaCO}_2 > 60$ mmHg) despite CPAP pressure of 7–8 cm H_2O and FiO_2 of 0.8 or recurrent episodes of apnea.^[8] Synchronized intermittent

mandatory ventilation mode was the main mode of ventilation in the neonates in our study. Lung protective ventilator strategies were employed as a standard practice. Pressure limited time cycled ventilation was used and the different ventilator parameters were individualized depending upon the particular disease and the lung mechanics and compliance. Arterial blood gases were analyzed regularly. In general, the parameters were: Tidal volume 6–10 ml/kg, positive end-expiratory pressure 4–8 mmHg, peak inspiratory pressure 18–28 mmHg, inspiratory time 0.25–0.5 s, and FiO_2 0.40–0.80. High frequency ventilation is not available at our hospital and was not used in any neonate. Relevant investigations such as complete blood counts, chest X-ray, kidney function test, liver function test, blood culture, cerebrospinal fluid analysis, blood sugar, serum calcium, cranial ultrasound, etc., were done and repeated as needed. All neonates with positive blood culture or diagnosed with pneumonia, meningitis, or urinary tract infection were considered to have sepsis. Shock was defined by clinical evidence of hypoperfusion in form of delayed capillary refill time (> 3 s), oliguria (urine output < 1 ml/kg/h), weak peripheral pulses, and hypotension in the presence of lactic acidosis. Ventilator-associated pneumonia (VAP) was defined as pneumonia that occurred 48–72 h or thereafter following endotracheal intubation and was characterized by the presence of a new or progressive infiltrate, symptoms and signs of infection, changes in sputum/endotracheal aspirate characteristics, and detection of a causative agent.^[9]

Thrombocytopenia was defined as platelet count $< 150,000/\mu\text{l}$. Absolute neutrophil count varies considerably in the immediate neonatal period and neutropenia was defined with respect to the normal reference ranges available from Manroe's charts.^[10] For very low birth weight infants, the reference ranges available from Mouzinho's charts^[11] were used. C-reactive protein (CRP) levels > 6 mg/dl were taken as positive. Hypoglycemia was defined as blood sugar < 50 mg/dl. The data was recorded on Microsoft Excel Worksheet and analyzed by GraphPad Instat 3.1 statistical program. Continuous variables were tested for normality using Kolmogorov and Smirnov method and Student's *t*-test, and Mann-Whitney U-test were used for comparison of normally distributed and nonparametric variables, respectively. Chi-square test and Fischer's exact test were used for categorical variables. $P < 0.05$ was considered significant. Those risk factors that were significant on univariate analysis ($P < 0.05$) were entered into a forward step-wise multivariable logistic regression model and independent risk factors were determined.

Results

During the study, 2980 neonates were admitted in total, out of which 300 were included in the study. One-hundred fifty-six (52%) were male and 144 (48%) were female. Respiratory distress syndrome (RDS) (31.1%), sepsis (22.7%), and birth asphyxia (18%) were the most common indications for ventilation [Table 1]. All the preterm neonates with gestational age <32 weeks or recurrent apneas or early features of RDS were given nasal CPAP therapy, and those who had a failure of nasal CPAP therapy (as defined above in methods section) were ventilated. Overall mortality in NICU during the study period was 12% and mortality in ventilated neonates was 43% (130/300). Disease-specific mortality was 33.3% in perinatal asphyxia, 44.7% in RDS, 26.7% in meconium aspiration syndrome (MAS), 60% in pneumonia, 64.7% in sepsis, and 54.5% in meningitis. Patients with sepsis had the highest disease-specific mortality (67.4%). The usual organisms isolated in cultures included *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterobacter*, and *Candida* species. Antibiotic usage was as per the antibiogram of our NICU generated by the Department of Microbiology on a regular basis.

Among continuous variables studied, birth weight, gestational age, and initial pH differed significantly between ventilated neonates who survived and those who died ($P < 0.05$). Maternal age, age at admission, and initial blood gas values (PO_2 , PCO_2) did not differ significantly in the two groups [Table 2].

Table 1: Indications for ventilation

Indication for ventilation**	Number of patients (%)	Survived (%)	Mortality (%)
Respiratory distress syndrome	94 (31.3)	52 (55.3)	42 (44.6)
Sepsis	68 (22.7)	24 (35.3)	44 (64.7)
Birth asphyxia	54 (18)	36 (66.6)	18 (33.3)
Meconium aspiration syndrome	30 (10)	22 (73.3)	8 (26.7)
Meningitis	22 (7.3)	10 (45.5)	12 (54.5)
Pneumonia	20 (6.7)	8 (40)	12 (60)

**Apnea and seizures could be primary or secondary to diseases mentioned; in how many cases patients needed ventilation due to these problems only was not clear, so they have not been included

Table 2: Predictors of mortality in ventilated neonates

Parameter	Non-survivors	Survivors	P
Birth weight (kg)	1965 ± 660.5	2630 ± 750.3	0.03*
Gestational age (weeks)	33.3 ± 3.9	36.2 ± 2.8	0.002*
Age at admission (h)	4 (1-144)	3 (1-720)	0.1003**
Maternal age (years)	29 (22-38)	30 (20-36)	0.909**
pH	7.18 (6.80-7.36)	7.24 (6.99-7.47)	0.0022**
PO_2 (mmHg)	46 (22-70)	46 (22-94)	0.265**
PCO_2 (mmHg)	46 (28-68)	52 (24-80)	0.0985**

*Student's t-test used; **Mann-Whitney U-test used

Among categorical parameters studied, birth weight <2.5 kg, prematurity <34 weeks, apnea, sepsis, shock, pulmonary hemorrhage, hypoglycemia, neutropenia, thrombocytopenia, and initial pH ≤7.1 were significantly associated with mortality. Resuscitation at birth, birth asphyxia, RDS, MAS, pneumonia, meningitis, seizures, intraventricular hemorrhage (IVH), VAP, pneumothorax, elevated CRP levels or hypoxemia, and hypercarbia had no significant relationship with mortality [Table 3].

The complications recorded in patients were shock, VAP, pulmonary hemorrhage, hypoglycemia, IVH, and pneumothorax. Of these, only shock, pulmonary hemorrhage, and hypoglycemia were significantly associated with mortality. Pulmonary hemorrhage occurred in cases of shock, disseminated intravascular coagulation, and pneumonia and in cases of RDS after surfactant therapy. VAP was detected in 36 patients of whom 12 died. The common organisms isolated in neonates with VAP were *S. aureus* and *K. pneumoniae*.

Multiple regression analysis was performed on data for 10 variables found significant on univariate analysis (gestational age <34 weeks, weight <2500 g, shock, apnea, sepsis, pulmonary hemorrhage, neutropenia, thrombocytopenia, and pH <7.1). Insignificant variables were eliminated to give final results as shown in Table 4. Gestational age <34 weeks, shock, neutropenia, pulmonary hemorrhage, and pH <7.1 were found to be significant independent predictors of fatality in mechanically ventilated neonates.

Discussion

Mortality among sick neonates in NICU is high,^[12] but mortality among mechanically ventilated neonates and outborn neonates referred for ventilation is even higher.^[2,13-15] In this study, mortality in ventilated neonates was 43.3%, which is comparable to mortality of 46% reported by Sangeeta *et al.*^[16] Hossain *et al.*^[17] and Mathur *et al.*^[15] reported higher figures of 70.6% and 74%, respectively.

Sex and age at admission did not have a statistically significant association with the outcome as was found by Kollef^[18] and Riyas *et al.*^[6] The outcome was however affected by the gestational age and birth weight of the neonate. Impact of low birth weight and prematurity on survival of neonates is known and reported by Mathur *et al.*^[15] and Hossain *et al.*^[17] as well.

We did not find a statistically significant difference in the mortality of neonates who were resuscitated

Table 3: Predictors of mortality in ventilated neonates

Parameter	Group 1			Group 2			RR	P
	Value	No	Mortality	Value	No	Mortality		
Birth weight (kg)	<2.5	176	90	≥2.5	124	40	1.59	0.001
Gestational age (weeks)	<34	130	78	>34	170	52	1.96	<0.0001
Resuscitation at birth	Yes	80	32	No	220	98	0.9	0.512
Apnea	Present	68	44	Absent	232	86	1.75	<0.0001
Birth asphyxia	Yes	54	18	No	246	112	0.73	0.132
RDS	Yes	94	42	No	206	88	1.85	0.80
MAS	Yes	30	8	No	270	122	0.59	0.055
Pneumonia	Yes	20	12	No	280	118	1.42	0.16
Sepsis	Yes	68	44	No	232	86	1.75	<0.0001
Pulmonary hemorrhage	Yes	42	36	No	258	94	2.35	<0.0001
Meningitis	Yes	22	12	No	278	118	1.28	0.275
Shock	Yes	116	86	No	184	44	3.1	<0.0001
Hypoglycemia	Yes	62	46	No	238	84	2.1	<0.0001
Seizures	Yes	54	24	No	146	106	1.03	0.88
IVH	Yes	18	10	No	282	120	1.3	0.533
Pneumothorax	Yes	6	4	No	294	126	1.56	0.41
VAP	Yes	36	12	No	164	118	0.75	0.21
CRP	Positive	60	28	No	240	102	1.1	0.564
Neutropenia	Present	56	36	Absent	244	94	1.65	0.0009
Thrombocytopenia	Present	50	48	Absent	250	82	2.93	<0.0001
pH	≤7.1	58	36	>7.1	242	94	1.6	0.0018
PO2	<50	200	88	≥50	100	42	1.05	0.862
PCO2	<60	218	98	≥60	82	32	1.15	0.58

CRP: C-reactive protein; VAP: Ventilator-associated pneumonia; IVH: Intra ventricular hemorrhage; MAS: Meconium aspiration syndrome; RAS: Respiratory distress syndrome

Table 4: Multiple logistic regression analysis of variables

Parameter	Adjusted OR	95% CI	P
Gestational age (weeks)	1.20	0.94-1.45	0.01
Shock	1.11	0.90-1.32	0.003
Pulmonary hemorrhage	0.96	0.89-1.05	0.033
Neutropenia	1.03	0.99-1.05	0.025
pH	0.98	0.94-1.01	0.044

OR: Odds ratio; CI: Confidence interval

as compared to those who were not resuscitated. It is a known fact that only cases of severe perinatal asphyxia have a high mortality and outcome is good in cases of mild and moderate perinatal asphyxia. Improved resuscitative measures at the time of birth and early referral for such babies seem to have led to the improvement in survival of all resuscitated and subsequently ventilated neonates.

Survival rate in our neonates for perinatal asphyxia and RDS was comparable to Hossain *et al.*^[17] and Anantharaj and Bhat^[19]. However, for diseases such as MAS and apnea survival rate in our NICU was slightly better as compared to Basu *et al.*,^[20] Anantharaj and Bhat^[19] and Riyas *et al.*^[6]

We saw a dismal outcome in neonates with sepsis. We had a survival rate of merely 35.3%. Increasing emergence of drug resistant organisms is changing the equations of survival in NICUs. Anantharaj and Bhat^[19] saw a survival rate of 46.1% in cases of sepsis. Respiratory

failure and need for mechanical ventilation in a septic neonate signifies severe advanced disease and is a bad prognostic indicator.

Pulmonary hemorrhage is a life threatening event in neonates and prognosis was dismal in our patients with this complication. Karthikeyan and Hossain^[4] and Anantharaj and Bhat^[19] also found a very poor outcome in neonates following pulmonary hemorrhage.

Shock had a significant impact on mortality in ventilated neonates in our study. Anantharaj and Bhat^[19] reported shock as the most common complication in ventilated neonates and also an important cause of mortality in their study. Shock represents an advanced stage of a disease process of varied etiologies and its relationship with mortality is understandable.

Hypoglycemia is common in sick neonates and predicted increased mortality in our study. Association of hypoglycemia with poor neurological outcome is well known, but we also saw poor survival in hypoglycemic ventilated neonates. It needs to be kept in mind that hypoglycemia was not the primary cause of death in all of these neonates. Survival in patients who developed IVH was better than what is reported by Basu *et al.*^[20] (44% vs. 0%). Early suspicion, routine screening for IVH, bed-side cranial sonography, and adherence to

proper preventive measures like sedation probably led to better outcome. Similarly, the outcome of patients who developed pneumothorax was better as compared to Anantharaj and Bhat^[19] Judicious ventilator strategies, proper sedation, timely extubation, and readily available X-ray and surgical facilities help to control this problem.

Neutropenia and thrombocytopenia had a statistically significant correlation with mortality in our patients. Prognostic significance of these parameters has been recognized by others as well.^[21-23] Acidosis (pH <7.1) at admission also predicted an increased mortality. A lower pH at admission indicates a larger time gap between the onset of events leading to the deterioration in the clinical status of the child and presentation to the healthcare facility. Thus, it will definitely have an impact on the outcome of the patients.

Limitations

Our study did not focus on the proportion of patients receiving noninvasive ventilation/CPAP who subsequently needed intubation and mechanical ventilation.

Furthermore, we were not able to study the factors determining the morbidity such as duration of NICU stay, mechanical ventilation, and hospital stay.

Conclusions

Identification of risk of fatality in ventilated neonates is compulsory in order to intervene early, decrease the mortality, and even for triage in resource limited settings. Among the numerous commonly available variables studied by us, weight <2500 g, gestation <34 weeks, initial arterial pH <7.1, shock, pulmonary hemorrhage, apnea, hypoglycemia, neutropenia, and thrombocytopenia were significant predictors of mortality in ventilated neonates.

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Conflict of interest

There are no conflicts of interest.

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