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Original Article

Predictors of Immediate Outcome in Neonates on Invasive Mechanical Ventilation

Durgesh Kumar[1*], Dinesh Kumar[1], Shashi Vinod[1], Indra Kumar Sharma[1], Rajesh Kumar Yadav[2], Rakesh Bahadur Singh[2]

1.Department of Pediatrics and Neonatology, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, India
2.Department of Anesthesiology, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, India

ABSTRACT

Background: Neonatal mechanical ventilation has contributed to a significant decline in neonatal mortality but is associated with various complications. It is necessary to identify the prognostic factors and their management to reduce the complications in mechanically ventilated neonates. Therefore, this study was designed to investigate the common indications, complications, and predictive factors associated to immediate outcomes in neonates from rural North India who received invasive mechanical ventilation.

Methods: This study includes all neonates admitted to the neonatal intensive care unit requiring invasive mechanical ventilation for at least 12 hours. All enrolled neonates were categorized into two groups: those who were successfully extubated were labeled as survivors, while those who did not survive during ventilation were classified as non-survivors. Clinical and ventilator parameters, as well as the occurrence of complications were analyzed to identify factors associated with outcomes in ventilated neonates.

Results: A total of 150 neonates who met the inclusion criteria were enrolled. The most frequent reason for ventilation was perinatal asphyxia. Among ventilated neonates, the mortality rate was 38.7%. When comparing survivor and non-survivor groups, a significant difference was observed in birth weight, gestational age, indication for ventilation, duration of ventilation, and blood acidosis (with a p-value < 0.05). Additionally, non-survivors experienced a higher prevalence of complications, including sepsis, shock, air leak syndrome, and pulmonary hemorrhage. Multivariate analysis revealed that gestational age less than 34 weeks, initial blood pH of 7.1 or lower, ventilation duration exceeding 72 hours, and the presence of sepsis, shock, or disseminated intravascular coagulation were significant independent predictors of mortality in ventilated neonates.

Conclusion: The mortality among ventilated neonates is still high in developing countries. Hospital acquired sepsis with shock is still the major complication among ventilated neonates. Early identification of risk factors for mortality and timely intervention may decrease the mortality.

Keywords: Mechanical ventilation, Neonates, Outcome, Sepsis

Introduction

Neonatal mortality constitutes almost two-thirds of infant mortality and half of under-five mortality in India (1). Assisted ventilation has become a crucial component of neonatal intensive care units (NICUs). While most infants in NICUs can be effectively treated with non-invasive oxygen therapy, a significant portion still requires invasive mechanical ventilation. This method has played a key role in the dramatic reduction of neonatal mortality over the past two decades (2). However, survival rates for neonates undergoing mechanical ventilation are higher in developed countries compared to developing nations, where the mortality rate among these newborns ranges

* *Corresponding author*: Durgesh Kumar, Department of Pediatrics and Neonatology, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, India. Email: drdurgeshk@gmail.com

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from 30-65% (3-9). Even with the availability of mechanical ventilation, the mortality rate among critically ill neonates remains alarmingly high in low-income countries. To enhance survival rates for ventilated neonates, it is essential to identify poor prognostic factors, complications associated with mechanical ventilation, and to manage these issues effectively.

The prognosis for sick neonates on mechanical ventilation is influenced by multiple factors, including gestational age, birth weight, co-existing clinical conditions, and complications related to the ventilation techniques used. There is a lack of comprehensive data on outcome predictors for neonates on mechanical ventilation in developing countries, including India. To reduce mortality in these infants, identifying risk factors is crucial. Therefore, this study aims to examine the various factors and complications that may impact the outcomes of neonates undergoing invasive mechanical ventilation in NICUs.

Methods

This cross-sectional study was conducted at the NICU of a government tertiary care research and teaching institute in North India from January 2020 to December 2021. The study included 192 consecutive neonates (aged 0 to 28 days) who required invasive mechanical ventilation for more than 12 hours, regardless of the indication. Neonates with major congenital anomalies, suspected metabolic disorders, those who had undergone surgery, referrals from outside the facility, and those who died within the first 12 hours of ventilation were excluded. Consequently, 150 neonates met the inclusion criteria and were included in the study. Ethical approval was granted by the institute's Ethical Committee (Ethical Committee Reference Letter No. 105/2019-20). After obtaining written and informed consent from the parents or guardians, a detailed history was collected, and a thorough examination was performed using a pre-designed and pre-structured proforma.

The indications for mechanical ventilation varied among the cases. The reasons for initiating mechanical ventilation included: (i) paO2 levels below 60 mmHg, (ii) persistent or recurrent apnea, (iii) gasping or inadequate respiration, (iv) oxygen saturation below 60% despite CPAP pressure of 7–8 cm H2O and FiO2 of 0.8, or recurrent episodes of apnea (9). Initially, all neonates were placed on synchronized intermittent mandatory ventilation (SIMV) mode, while pressure support ventilation mode was utilized for weaning. The typical initial ventilator settings included: tidal volume of 4-6 ml/kg, positive end-expiratory pressure of 4–8 mmHg, peak inspiratory pressure of 18–28 mmHg, inspiratory time of 0.25–0.5 seconds, and FiO2 ranging from 0.40 to 0.80 (10). Vital signs were monitored every two hours for all ventilated neonates, with daily arterial blood gas analysis and other necessary tests conducted until extubation was planned. Relevant diagnostic investigations were also performed. Management followed the standard protocol of our NICU, including intravenous fluids adjusted for the neonate's weight and postnatal age. Empirical first-line antibiotics were administered based on the NICU's antibiotic policy and adjusted according to clinical conditions and culture results. Enteral feeds with expressed breast milk were introduced once the neonate was hemodynamically stable. Ventilator settings were tailored to the underlying conditions and acid-base balance. Weaning was attempted when clinical improvement was evident, with stable vital signs and normal blood gas results. The duration of ventilation and any complications encountered were documented. The neonates were categorized into two groups: survivors, who were successfully extubated without the need for re-intubation, and non-survivors, who either died after 12 hours of mechanical ventilation or within 48 hours of extubation. Complications recorded included sepsis (positive blood culture or diagnosed with meningitis or urinary tract infection after more than 48 hours of mechanical ventilation), shock (weak peripheral pulses with capillary refill time over 3 seconds and urine output less than 1 ml/kg/h), disseminated intravascular coagulation (bleeding symptoms with PT-INR above 1.7, fibrinogen level below 100 mg/dL, and elevated fibrin degradation products), air leak syndrome (escape of air from an air-containing cavity to a non-air-containing cavity), ventilator-associated pneumonia (VAP, pneumonia occurring after more than 48 hours of mechanical ventilation with new or progressive infiltrate), pulmonary hemorrhage (blood extravasation into airways or lung parenchyma), and intra-ventricular hemorrhage (bleeding inside or around the brain ventricles). The NICU management protocols of our institution were followed for treating these ventilator-related complications.

All collected data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 23. Categorical variables were reported as numbers and percentages, while continuous

variables were expressed as means with standard deviations. The Chi-square test was used to assess associations between two or more categorical variables, with a p-value of <0.05 considered statistically significant. Variables identified as significant in the univariate analysis were further examined using multivariate logistic regression to determine independent predictors of mortality.

Ethical approval

Ethical approval was granted by the institute's Ethical Committee (Ethical Committee Reference Letter No. 105/2019-20).

Results

A total of 150 neonates met the inclusion criteria and their data were analyzed. Table 1 provides an overview of the demographic characteristics of these neonates and their survival outcomes. The average age at which neonates were placed on the ventilator was 3.69±5.6 days. The male-to-female ratio in the study was 1.43:1. The most common reason for mechanical ventilation was perinatal asphyxia, followed by respiratory distress syndrome and sepsis. The average duration of mechanical ventilation was 62.28±23.7 hours. Among the 150 neonates, 92 (61.3%) were successfully weaned from the ventilator and survived.

Table 2 depicts the comparison of baseline parameters in relation to survival and non-survival of neonates from ventilator. A statistically significant difference was noted for variables of birth weight, gestational age, acidosis, indication of mechanical ventilation and duration of mechanical ventilation.

In the present study, one or more complications were observed in 108 (72%) ventilated neonates. The most common complication encountered was sepsis in 93 (63.3%) followed by shock in 77 (51.3%). When we compared these complications between survived and non-survived neonates, a statistically significant difference was found for

Table 1. Study Population characteristics

Variable (n= 150)	Values
Mean Age at which neonate was put on ventilator (in days)	3.69±5.6
Gender Ratio (M:F)	1.43 : 1
Birth Weight (in grams)	2148±741
Gestational age (in weeks)	35.69±4.82
Full term	94 (62.67%)
Preterm	56 (37.33%)
Appropriate for gestational age (AGA)	115 (76.67%)
Small for gestational age (SGA)	29 (19.33%)
Large for gestational age (LGA)	5 (3.33%)
Primary indication of invasive mechanical ventilation	
Birth asphyxia	57 (38.0%)
Respiratory distress syndrome	39 (26.0%)
Neonatal Sepsis	26 (17.33%)
Meconium aspiration syndrome	12 (8.00%)
Acute bacterial Meningitis	09 (6.00%)
Pneumonia	07 (4.67%)
Mode of invasive mechanical ventilation used	
Synchronized intermittent mandatory ventilation (SIMV)	114 (76.00%)
Assisted control (AC)	29 (19.33%)
Pressure support (PSV)	7 (4.67%)
Average duration on Mechanical ventilation (in hours)	62.28±23.7
Outcome	
Successfully weaned off from ventilator (Survived)	92 (61.3%)
Non-survivor	58 (38.7%)

Table 2. Predictors of mortality in ventilated neonates

Parameter (n= 150)	Weaned off (n=92)	Non survived (n=58)	p value
Birth weight			
<2000 gm	50 (33.3%)	38 (25.3%)	0.043
≥2000 gm	42 (28.0%)	20 (13.3%)	
Gestational age			
< 34 weeks	38 (25.3%)	28 (18.7%)	0.005
≥ 34 weeks	54 (36.0%)	30 (20.0%)	
Weight for gestational age			
Small for gestational age (SGA)	9 (6.0%)	6 (4.0%)	
Appropriate for gestational age (AGA)	79 (52.7%)	50 (33.3%)	0.081
Large for gestational age (LGA)	4 (2.7%)	2 (1.3%)	
Primary indication of invasive mechanical ventilation			
Birth asphyxia	35 (23.3%)	22 (14.7%)	
Neonatal Sepsis	23 (15.3%)	16 (10.7%)	
Respiratory distress syndrome	15 (10.0%)	11 (7.3%)	
Meconium aspiration syndrome	8 (5.3%)	4 (2.7%)	0.034
Acute bacterial Meningitis	6 (4.0%)	3 (2.0%)	
Pneumonia	5 (3.3%)	2 (1.3%)	
Initial pH			
≤ 7.1	61 (40.7%)	38 (25.3%)	0.002
> 7.1	31 (20.7%)	20 (13.3%)	
PaO2 (mm of Hg)			
> 50	48 (32.0%)	32 (21.3%)	0.648
≤ 50	44 (29.3%)	26 (17.3%)	
PaCO2 (mm of Hg)			
> 60	41 (27.3%)	24 (16.0%)	0.325
≤ 60	51 (34.0%)	34 (22.7%)	
Duration of mechanical ventilation (Hrs)			
> 72	26 (17.3%)	18 (12.0%)	0.009
≤ 72	66 (44.0%)	40 (26.7%)	

Table 3. Outcome of ventilated neonates in relation to complications (n=150)

Complication	No. of patients with complication (%)	No. of survived neonates after complication (%)	No. of neonates not survived after complication (%)	Unadjusted OR (95% CI)	p value
Sepsis	93 (63.3%)	63 (42.0%)	30 (20.0%)	0.493 (0.25 - 0.97)	<0.001
Shock	77 (51.3%)	51 (34.0%)	26 (17.3%)	0.653 (0.34 - 1.27)	<0.001
DIC	23 (15.3%)	18 (12.0%)	5 (3.3%)	0.388 (0.14 - 1.11)	<0.001
Air leak syndrome	9 (6.0%)	5 (3.3%)	4 (2.7%)	1.29 (0.33 - 5.01)	<0.001
VAP	12 (8.0%)	7 (4.7%)	5 (3.3%)	1.15 (0.35 - 3.80)	0.086
Pulmonary hemorrhage	7 (4.7%)	3 (2.0%)	4 (2.7%)	2.20 (0.47 - 10.20)	<0.001
Intra-ventricular hemorrhage	4 (2.7%)	1 (0.7%)	3 (2.0%)	4.96 (0.50 - 48.91)	0.063

DIC: disseminated intravascular coagulation, VAP: ventilator-associated pneumonia

sepsis, shock, disseminated intravascular coagulation (DIC), air leak syndrome and pulmonary hemorrhage (Table 3).

Multivariate analysis revealed that gestational age <34 weeks, initial blood pH ≤ 7.1, mechanical ventilation duration >72 hours, sepsis, shock, and disseminated intravascular coagulation were significant independent predictors of mortality in neonates receiving mechanical ventilation (Table 4).

Table 4. Multivariate logistic regression for prediction of mortality

Analysed Parameter (n=150)	p-value	Adjusted OR	95% Confidence Interval	
			Lower	Upper
Birth weight (<2000 gm)	0.091	0.851	0.681	7.847
Gestational age (<34 weeks)	<0 .001	0.398	0.139	1.192
Initial pH (≤7.1)	0.021	0.755	0.350	1.629
PaO2 (< 50 mm of Hg)	0.971	0.987	0.482	2.022
PaCO2 (> 60 mm of Hg)	0.094	0.828	0.401	1.707
Duration of mechanical ventilation (>72hr)	0.009	1.123	0.518	2.437
Sepsis	0.004	0.304	0.135	0.684
Shock	0.034	0.429	0.196	0.940
DIC	0.034	0.286	0.090	0.910
Air leak syndrome	0.879	1.130	0.236	5.404
VAP	0.687	1.312	0.351	4.897
Pulmonary hemorrhage	0.353	2.187	0.419	11.419
Intra-ventricular hemorrhage	0.206	4.602	0.432	48.994

DIC: disseminated intravascular coagulation, VAP: ventilator-associated pneumonia

Discussion

The use of neonatal mechanical ventilation has led to an overall improvement in the survival rate of critically ill newborns in the NICU. In this study, 61.3% of neonates were successfully weaned off the ventilator and survived. Perinatal asphyxia was identified as the most common reason for initiating mechanical ventilation. A comparison of baseline parameters between survivors and non-survivors revealed significant differences in birth weight, gestational age, duration of mechanical ventilation, and acidosis. Sepsis was the most frequently encountered complication during mechanical ventilation.

There are fewer studies to compare within our country, so data from other developing countries were compared. Fatality rate recorded in the study was slightly lower than the other studies from developing countries but higher than the developed countries (5, 9). Difference in the outcome could be attributed to the fact that the study was carried at our level-3 NICU with all the facilities including surfactant therapy and total parenteral nutrition were available for

management of critically ill neonates. But due to limitation of manpower (doctor: patient ratio) and technological advances, mortality rate was higher when compared to developed countries.

In our study, the most frequent indication for mechanical ventilation was birth asphyxia, followed by respiratory distress syndrome, sepsis, and meconium aspiration syndrome, which aligns with the findings of Riyas et al. (7) and Thakur et al. (10) Conversely, Rai et al. (11) and Thakkar et al. (12) identified sepsis and respiratory distress syndrome, respectively, as the most common indications for ventilation. As our institute is situated in periphery we cater to rural population where due to lack of information/ knowledge and transfer facilities, deliveries are conducted at home by untrained birth attendant, also patients are referred late to the institute that further contributes to birth asphyxia.

In the prediction of mortality for ventilated neonates, age and gender did not significantly influence outcomes. In contrast, low birth weight and prematurity were significantly associated with increased mortality. These findings are consistent with those reported by Mathur et al. (13) and Othman et al. (14) Low blood pH before initiation of ventilation and duration of mechanical ventilation were also found to be significant predictors that negatively affect outcome. Similar findings were observed by Monsef et al (15). An initial low pH reflects the severity of underlying diseases or the time interval between events and the deterioration of the baby's clinical condition. Consequently, it significantly influences the disease outcome. Interestingly, the initial paO2 value, while measured, did not show a significant association with poor outcomes. This observation suggests that pre-existing acid-base imbalances, already present before ventilation play a crucial role in determining overall outcomes. Early identification of such disturbances could potentially prevent organ damage and improve overall neonatal outcomes (13,16).

Ventilation related complications were present in 72% cases and these complications were significantly associated with adverse outcomes in our study. These complications might be prevented by early initiation of ventilation before beginning of organ damage. The most frequent complication observed was sepsis followed by shock in our study. Yadav et al (17) and Regmi et al (18) reported sepsis and shock respectively as the most prevalent complication in ventilated neonates. Applying minimal intervention and using antibiotics judiciously could potentially decrease its occurrence. The incidence of ventilator associated pneumonia (VAP) and pulmonary air leak was quite low in this study noticed only in 8% and 6% of ventilated neonates respectively whereas Petdachai et al and Torres-Castro et al reported ventilator associated pneumonia in 50% ventilated neonates (19-20). The lower incidence of these complications in our study may be associated with under diagnosis of these complications.

Our study has certain limitations as well, including a small sample size and conducted at a single center. Most of the patients in this study were kept on noninvasive ventilation for a variable duration before receiving invasive mechanical ventilation which might have variable effect on the outcome. This was a cross-sectional study hence no follow-up could be traced.

Conclusion

Continuous monitoring and early identification of complications are mandatory to decrease the mortality in neonates on mechanical ventilation. Among the analyzed variables prematurity, initial blood pH, duration of mechanical ventilation and complications during ventilation emerged as significant independent predictors of neonatal outcomes. These predictors would be useful to prognosticate the admitted neonates and improve the overall functioning and outcome of NICUs especially in low-income countries.

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Conflicts of interest

The authors declare there is no conflict of interest.

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