Original Article

Predictors of Fatality in Neonates Requiring Mechanical Ventilation

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Manuscript received: July 1, 2003, Initial review completed: September 3, 2003, Revision accepted: February 22, 2005.

Objective: *To evaluate initial arterial blood gas, pulmonary pressures, pulmonary mechanics (compliance and resistance), pulmonary volumes, oxygenation indices and serum carotenoid levels as predictors of fatality in mechanically ventilated neonates.* ***Design:*** *Cross-Sectional.* ***Setting:*** *Referral neonatal unit of a teaching hospital.* ***Subjects:*** *83 mechanically ventilated outborn neonates.* ***Methods:*** *83 neonates consecutively put on mechanical ventilator from March to December 2001 were enrolled in the study. The mechanical ventilator used was pressure-limited time cycled ventilator with facility for online measurement of volumes and pulmonary mechanics. Arterial blood gas after half an hour of initiation of mechanical ventilation and initial pulmonary pressures, pulmonary compliance, resistance and duration of mechanical ventilation were recorded in a pre-structured proforma. Initial serum carotenoid levels were also measured using spectrophotometric method. The neonates were regularly followed up for outcome. Multiple logistic regression analysis was done to find out the predictors of fatality for those variables that were significantly associated with outcome on univariate analysis.* ***Results:*** *On univariate analysis weight (< 2000 g), gestational age <34 weeks, pH <7.3, duration of mechanical ventilation <72 hours, a/A <0.25, compliance <1 mL/cmH_2O, fraction of inspired oxygen (FiO_2) >60%, oxygenation index >10, AaDO2 >250 and serum carotenoid levels < 100 µg/dL were significantly associated with fatality in neonates requiring mechanical ventilation. However, on multiple regression analysis only FiO_2, gestational age and serum carotenoids < 100 µg/dL were found to be independent predictors of fatality.* ***Conclusions:*** *Initial FiO_2 > 60%, gestational age <34 weeks and initial serum carotenoid levels < 100 µg/dL were independent predictors of fatality in neonatal mechanical ventilation. Even in a setting with high fatality rates, high risk of mortality in mechanically ventilated neonates can be identified.*

Keywords: *Fatality, FiO_2, Gestational age, Mechanical ventilation, Neonates, Serum carotenoids.*

A large number of neonates in neonatal intensive care unit require mechanical ventilation. These mechanically ventilated neonates have a high fatality(1-4). For reduction in fatality in this group of neonates, identification of risk factors is important. Earlier reports on fatality in mechanically ventilated neonates are simple correlation studies done in an uncontrolled way. Lower levels of serum Vitamin A are associated with poor outcome in neonates with severe respiratory failure(5). There is a paucity of reports on risk factors associated with fatality in mechanically ventilated neonates using multiple regression analysis to establish risk factors for fatality with adjustment for

potential confounders. The present study was therefore designed to evaluate the risk factors associated with fatality in mechanically ventilated neonates using multiple regression analysis.

Subjects and Methods

The study was conducted on neonates admitted to the Referral Neonatal Unit of Lok Nayak Hospital, New Delhi between March 2001-December 2001. The unit caters to neonates referred from hospitals of Delhi and surrounding states or born at home and transported to the hospital directly by the relatives. All 163 neonates consecutively put on mechanical ventilator were enrolled in the study. Eighty neonates who required ventilation for surgical malformations and terminally ill neonates in multi-organ dysfunction (evidence of disseminated intra vascular coagulation along with altered renal hepatic or neurologic dysfunction) were excluded from the study. Eighty-three neonates thus finally constituted the study population. The mechanical ventilator used was pressure-limited time-cycled ventilator with facility for on line measurement of volumes and pulmonary mechanics. (Drager Babylog 8000 plus and Infant Star 500 star Sync with Star Trac). Only one neonate had received antenatal steroids. All neonates were continuously monitored electronically for temperature, pulse, respiration and oxygen saturation.

The indications for neonatal mechanical ventilation were (*i*) PaO_2 <50 mm of Hg or SaO_2 <85% with FiO_2 requirement more than 70%, (*ii*) $PaCO_2$ >55 mm of Hg with pH <7.2 or $PaCO_2$ >60 mm of Hg and (*iii*) Intractable apneic spell. Observations at the time of initiation of mechanical ventilation included (*i*) Arterial blood gas analysis done half hour after initiation of mechanical ventilation, (*ii*) Initial pulmonary pressures: peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), mean airway pressure (MAP), (*iii*) pulmonary compliance, pulmonary resistance, (*iv*) tidal volume, minute ventilation, initial pulmonary pressures, pulmonary mechanics and pulmonary volumes were displayed on the ventilator. Oxygen saturation was monitored and maintained between 92 and 95%, (*v*) Oxygen indices (PaO_2/P_AO_2 or the a/A ratio, $AaDO_2$, Oxygenation index), (*vi*) Duration of mechanical ventilation, and (*vii*) Serum carotenoid levels measured by spectro-photometric method(6,7).

The continuous variables were analyzed using student '*t*' test and proportions by Chi square test or Fischer test. Probability of 5% was considered significant. Man Whitney U test statistics was used where standard deviations were more than half of mean, where negative values are absurd.

The factors found to be of statistical significance on univariate analysis were subsequently subjected to a stepwise multiple logistic regression analysis (backward model) using computer software SPSS to evaluate the independent factors associated with fatality in mechanically ventilated neonates.

Results

Eighty-three neonates were enrolled for the study. Causes of respiratory insufficiency requiring mechanical ventilation included apnea in 32 (38.6%), pneumonia in 28 (33.7%), meconium aspiration syndrome in 14 (16.9%), Hyaline membrane disease in 7 (8.4%) and congenital heart disease in 2 (2.4%). Forty six neonates were home delivered and 52 were males. At admission, 72 neonates were unstable with respect to temperature, oxygen saturation, perfusion and blood sugar. Complications of mechanical ventilation included pulmonary air leaks in

13 and pneumonia in 20 neonates. Retinopathy of prematurity was present in none. Out of 83 mechanically ventilated neonates enrolled for the study, 62 (74%) died. Factors significantly different in non-survivors were weight, gestational age, fraction of inspired oxygen, peak inspiratory pressure, compliance, $AaDO_2$, a/A, oxygenation index (OI) and serum carotenoid levels (*Table I*). Weight (<2000 grams), gestational age (<34 weeks), pH <7.3, duration of mechanical ventilation <72 hours, fraction of inspired oxygen (>60%), compliance (<1 mL/mm of Hg), a/A <0.25, $AaDO_2$ >250, oxygenation index >10 and serum carotenoid levels <100 µg/dL were significantly associated with fatality in neonates requiring mechanical ventilation (*Table II*). However, sex, age at initiation of ventilation, PaO_2, $PaCO_2$, base excess, PIP, PEEP, MAP, minute volume, tidal volume and resistance were not associated with fatality.

Multiple regression analysis was done on data from 80 cases (3 cases for which data on pulmonary compliance was not available were excluded from the regression model). Initially 7 variables found significant on univariate analysis (Gestational age <34 weeks,weight <2000 grams, pH <7.3, S. Carotenoids <100 µg/dL, Compliance <1 mL/cm of water, a/A < 0.25 and FiO_2 >60%) were put in stepwise backward model. On multiple regression analysis, insignificant variables were eliminated to give final results as shown in *Table III.* Gestational age <34 weeks, serum carotenoids <100 µg/dL and FiO_2 requirement >60% were found to be significant independent predictors of fatality in mechanically ventilated neonates.

Discussion

Mechanically ventilated neonates have a high fatality(1-4). The fatality is even higher in the small number of tertiary referral neonatal units receiving out born neonates. Eighty seven per cent neonates in the present study were destabilized at admission with reference to temperature, oxygen saturation, tissue perfusion and blood sugar. The fatality in these neonates would not lower till a proper network of neonatal services in district hospitals linked to regional referral neonatal units is established. Unfortunately there is a paucity of data on mechanical ventilation in out born neonates and the number of units catering to these neonates is grossly inadequate.

The present study highlights the identification of FiO_2, gestational age and serum carotenoid levels as significant independent predictors of fatality in mechanically ventilated neonates. In the present study low serum carotenoid levels were the most significant risk factors for fatality in mechanically ventilated neonates. β-carotene and other carotenoids are endogenous non-enzymatic lipid phase anti-oxidants. It is already known that low birth weight infants with low serum vitamin A levels are at higher risk of developing chronic lung disease and bronchopulmonary dysplasia(5). The reference range of serum carotenoids is 50-250 µg/dL in adults(6). Data on reference range of serum carotenoids in neonates is lacking. Retinol has an essential role in the respiratory tract epithelial cell differentiation and integrity (8,9). Deficiency state of vitamin A is characterized by the loss of cilia and the development of squamous metaplasia in the respiratory tract, changes also found in the bronchopulmonary dysplasia(10,11). Studies correlating initial serum carotenoid and serum vitamin A levels with fatality in mechanically ventilated neonates are lacking. Further studies are required to evaluate the effect of vitamin A supplementation in reducing fatality in mechanically ventilated neonates in India.

Gestational age and FiO_2 requirement

TABLE I–*Descriptive Statistics of the Survivors and Non-survivors*

Parameter	Non-survivors Median (Range)	Survivors Median (Range)	p-value Student 't' test
Weight (g)	1810 (680 - 3720)	2495 (850- 3865)	0.006
Gestational age (wks)	35 (26- 40)	38 (32-42)	0.001
Age at initiating ventilation (hrs)	76 (6-512)	84 (12- 608)	0.661
Arterial pH	7.26 (6.8-7.49)	7.37 (6.9- 7.55)	0.269
Arterial Base excess	–7.2 (–7.0 - -13.6)	–10 (–3.5 - –5.7)	0.262
PaO_2 (mmHg)	89 (39- 168)	81 (41-256)	0.014
$PaCO_2$ (mmHg)	38.6 (26-68)	37.7 (21-46)	0.514
Duration of MV (hrs)	56 (8-296)	72 (4-600)	0.514
FiO_2 (%)	70 (30-100)	50 (30-100)	0.00
PIP	20 (13-28)	18 (12-24)	0.027
PEEP	4 (3-5)	3 (3-4)	0.856
MAP	7.2 (4.3-15)	8.3 (3.8-10.8)	0.073
Compliance(ml/cm H_2O)	0.82 (0.16-1.8)	1.6 (1.2-2.52)	0.001
Minute ventilation (mL/Kg)	272 (85.8-1500)	320 (124-1615.65)	0.501
Tidal volumes (mL/Kg)	6.7 (2.67-32)	10.8 (4.3-26)	1.0
$AaDO_2$	272 (148-658)	231 (140-425)	0.004
a/A	0.35 (0.17-0.66)	0.26 (0.1-0.39)	0.017
Oxygenation index	8.3 (4.8-45)	4.66 (3.1-25.8)	0.003
Resistance	98 (67-208)	118 (60-182)	0.071
S. carotenoids (µg/dL)	60 (20-142)	120 (108-242.6)	0.000

TABLE II –*Correlation of Variables with Outcome in Mechanically Ventilated Neonates.*

Parameter	Group I	Fatality No.(%)	Group II	Fatality No.(%)	P-value	Odds ratio
Weight (g)	≤ 2000	39 (87)	>2000	44(64)	0.018	3.9 (1.3-11.9)
Gestational age (wks)	≤34	28(96)	>34	55(64)	0.001	15.4 (1.9-122.)
Initial pH	≤7.3	44(88)	>7.3	39(59)	0.003	5.4 (1.75-16.7)
Duration of MV (hrs)	≤72	66(82)	>72	18(47)	0.003	0.2 (4-108)
FiO_2 (%)	≤60	53(62)	>60	30(90)	0.018	4.6 (1.23-17.3)
Compliance mL/cmH_2O *	≤1.0	46(83)	>1.0	34(30)	0.000	0.09 (0.02-0.38)
$AaDO_2$	≤250	30(27)	>250	50(84)	0.015	3.41 (1.2-9.55)
a/A	≤0.25	49(88)	>0.25	34(56)	0.001	6.4 (0.006-20.8)
Oxygenation Index	≤10	65(69)	>10	18(94)	0.059	7.55 (0.94-60.6)
Serum carotenoid level (µg/dL)	≤100	49(99)	>100	34(47)	0.000	16.6 (0.003-400)

* Data on compliance is not available in 3 cases.

Table III–*Multiple Logistic Regression Analysis of Variables (n = 80).*

Predictor variables	Crude Odds ratio(95%CI)	Adjusted Odds ratio(95%CI)	P-value
Gestational age <34 wks	1.21 (0.91-1.61)	1.26 (1.04- 1.53)	0.02
S carotenoids <100 µg/dL	1.01 (1.00-1.02)	1.01 (1.01-1.02)	0.001
FiO_2 >60%	0.97 (0.94-1.00)	0.97 (0.94-1.00)	0.047

were the other independent risk factors for fatality in our study. These parameters available routinely can be identified to predict the risk of fatality in mechanically ventilated neonates. Earlier studies have also identified gestational age <34 weeks as a risk factor for fatality(12-14). FiO_2 requirement reflects the severity of respiratory failure. All oxygen indices like OI, $AaDO_2$ and a/A are dependent on it(15). Ortega and coworkers have shown significant association between a/A ratio and adverse outcome(16). Gilbert and Keighley have shown arterial alveolar oxygen tension ratio as a more stable index of gas exchange

Key Messages

- The significant risk factors for fatality in mechanically ventilated neonates on univariate analysis are weight, gestational age, pH, duration of mechanical ventilation, a/A, compliance, FiO_2, oxygenation index, $AaDo_2$ and serum carotenoid levels.
- On Multiple regression analysis FiO_2, gestational age and serum carotenoid levels less than 100 µg/dL were independent predictors of fatality.

than the alveolar arterial oxygen tension difference with changing values of inspired oxygen concentration(17). These indices are dependent on FiO_2, which thus is a good indicator of prognosis.

In conclusion, risk of fatality can be identified in mechanically ventilated neonates. Main limitation of the present study was that all risk factors could not be taken in the regression model because of sample size. There is an urgent need for further studies with larger sample size to identify risk factors before the neonate reaches a critical stage. Newer modalities of mechanical ventilation like high frequency oscillatory ventilation need evaluation using high risk factors as indicator of severity. Further studies are required to evaluate the effect of vitamin A supplementation on the outcome of mechanical ventilation.

Contributors: NBM conceived and designed the study, interpreted the data, was involved in finalising the draft and will act as guarantor of the paper; PG and TKM were involved in acquisition and analysis of the data and drafting and final approval of the article.

Funding: None.

Competing interests: None stated.

REFERENCES

1. Nangia S, Saili A, Dutta AK, Gaurvani MS, Seth A, Kumari S. Neonatal mechanical ventilation. Experience at a level II care centre. Indian J Pediatr 1998; 65: 291-296.
2. Mathur NC, Kumar S, Prasanna AL, Sahu UK, Kapoor R, Roy S, *et al*. Intermittent positive pressure ventilation in a neonatal intensive care unit: Hyderabad experience. Indian Pediatr 1998; 35: 349-353.
3. Singh M, Deorari AK, Paul VK, Mittal M, Shankar S, Munshi U, *et al*. Three year experience with neonatal ventilation from a tertiary care hospital in Delhi. Indian Pediatr 1993; 30: 783-789.
4. Johnson D, Natalie CM, Grobstein R, Walsh D, Daily WJR, Sunshine P. Prognosis of children surviving with the aid of mechanical ventilation in the newborn period. Arch Dis Child 1978; 34: 546-570.
5. Kaplan LA. Determination of serum vitamin level. *In:* Clinical Chemistry Eds. Kaplan LA. 3rd edn. Philadelphia, CV Mosby Company1996; pp 1401-1403.
6. Bradley DW, Hornbeck CL. A clinical evaluation of an improved TFA micromethod for plasma and serum vitamin A. Biochem Med 1973; 7: 78-86.
7. Inder TC, Graham PY, Winterboum CC, Auctin NC, Derlow DA. Plasma vitamin A levels in the very low birth weight infants relationship to respiratory outcome. Early Human Dev 1990; 52: 155-160.
8. Blackfem RD, Wolback SB. Vitamin A deficiencies in infants. J Pediatr 1933; 3: 679-684.
9. Carpo JD, Barry BE, Blackfem M, Weibel ER. Cell number and cell characteristies of the normal human lung. Am Rev Respir Dis 1982;125: 740-748.
10. Northway WH, Rosaw RC, Portor DY. Pulmonary disease following respiratory therapy of hyaline membrane disease

bronchopulmonary dysplasia. N Eng J Med 1967; 276: 357-361.

11. Wharton BA. Nutrition and feeding of preterm infants. Oxford, Blackwell Scientific Publications, 1987.

12. Murdock AI, Linsao L, Redi MM , Sutton MD, Tilak KS, Ulan OA, *et al*. Mechanical ventilation in the respiratory distress syndrome: A controlled trial. Arch Dis Child 1970; 45: 624-632.

13. Kishan l, Valdez J, Mir NA, Elzouki AY. Mechanical ventilation in newborn infants. Afr J Med Sci 1988; 17: 83-88.

14. Lindroth M, Svenningsen NW, Ahlstrom H. Evaluation of mechanical ventilation in newborn infants. Acta Pediatr Scand 1980; 69: 143-149

15. Harris TR, Wood BR. Physiologic principles. *In:* Assisted ventilation of the neonate. Eds Goldsmith SP, Karotkin EH. 3rd edn. Philadelphia, WB Saunders,1996; p 21-68.

16. Ortega M, Ramos AD, Platzker AC, Atkinson JB, Bowman CM. Clinical and laboratory observations. Early prediction of ultimate outcome in newborn infants with severe respiratory failure. J Pediatr 1988,113:744-746.

17. Gillbert R, Keighley JF. The arterial alveolar oxygenation ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. Am Rev Resp Dis 1974;109: 142-145.