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Profile and outcome of neonates requiring ventilation: The Kerala experience.

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Abstract

Mechanical ventilation has become an indispensable part of neonatal intensive care. There are many neonatal units both in the Government and private sector in Kerala, India offering this facility but data regarding profile and outcome of ventilated babies are limited. This study was undertaken to assess the indications, outcome, complications and factors affecting outcome in neonates requiring ventilation. This is a retrospective study of the first 100 ventilations undertaken in Government Medical College, Ernakulam. The indications, outcome, clinical and ventilator parameters were analysed. Out of 100 ventilated babies, the overall survival was 75%. Of the ventilated, 72 were preterm, 25 were term and 3 were postterm babies. The commonest indication for ventilation was hyaline membrane disease (HMD). Higher birth weight and gestational age were significantly associated with a better outcome. The best outcome was for birth asphyxia with 100% survival. The age at initiation of ventilation was significantly lower in the survivors. Complications which were independently predictive of death were disseminated intravascular coagulation (DIC) and pulmonary hemorrhage.

Keywords: Neonatal ventilation, Neonatal respiratory failure, Outcome, Complications, Mortality predictors

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Introduction

Mechanical ventilation was started in the West in early 60's with the establishment of neonatal intensive care units. In India, neonatal ventilation was started in the early 80's and in present day neonatal practice the NICU is incomplete without a ventilator. Survival outcome in various studies have ranged from 24.5% to 67.9% [1-7] among mechanically ventilated neonates in the era when surfactant was not widely used whereas it was 58% in a more recent study [8]. Reported studies from the developed countries quote a survival rate of 91% [9]. Neonatal ventilation is offered in many level 3 neonatal units in the private and government sector in Kerala but there is dearth of data regarding the profile and outcome of these babies. Hence this study was undertaken to identify the indications, co-morbidities, predictors of mortality, complications and outcome of neonates requiring ventilation at Government Medical College, Ernakulam, Kerala, India.

Material and Methods

This is a retrospective study of the first 100 neonatal ventilations at Government Medical College, Ernakulam with data being obtained by case file review. Government Medical College, Ernakulam, Kerala (formerly Co-operative Medical College, Kochi) is one of the 7 Government Medical Colleges in Kerala. This Medical College Hospital is the only tertiary neonatal unit in the Government Sector in the District and is a referral centre for patients from the surrounding Taluk and District General Hospital. The unit being in the government sector, is often constrained to work as a low resource setting in order to maximize health care delivery to the vast numbers of the economically disadvantaged who access its services. The unit is staffed by a 3 nurses per shift with a theoretical nurse: patient ratio of 1:3, which on many occasions is higher owing to higher patient load. The unit is covered by 1 senior paediatrician trained in neonatology and 2 junior paediatricians during the day. During emergency hours, one paediatrician covers all the areas namely, paediatric casualty, general paediatrics, NICU, PICU and the labour room.

The study was over a 6 year period (January 2008 - December 2013). Approval was obtained from the Institute research and ethical committee. During the study period the total NICU admissions was 2826 out of which 100 neonates were ventilated. All the 100 neonates required mechanical ventilation for neonatal respiratory failure of

pulmonary or central cause for more than 4 hours. All babies (both inborn and outborn) ventilated were included in the study. Babies with congenital cardiac disease and surgical conditions other than congenital diaphragmatic hernia (CDH) were excluded from the study.

Standard case definitions as per the National Neonatal Perinatal database criteria were used for diagnosis for all conditions described in this paper [10].

The maternal details, perinatal details, mode of delivery, Apgar score, resuscitation details, cord blood gas (if inborn), admission blood gas (if outborn) , birth weight or admission weight, Downes score at birth, Downes score before ventilation, time when respiratory distress was noted, time when it worsened, age of initiation of ventilation were recorded in a predefined proforma. All babies were treated according to the unit protocol which was based on standard protocols of neonatal management. All babies with neonatal respiratory failure who were ventilated, were screened for sepsis with blood routine examination, peripheral smear, band cell count estimation, C reactive protein, blood culture and chest X ray. Cerebrospinal fluid examination was done only if sepsis was diagnosed clinically or by laboratory methods. The babies were commenced on intravenous fluids which were titrated daily based on the daily weight, urine output, postnatal age and electrolyte status. Trophic enteral feeds were introduced using expressed breast milk as soon as it was available. Crystalline penicillin and gentamicin were used as the first-line antibiotics. Second line antibiotics were Cefotaxime and Amikacin. Other antibiotics were added only based on the culture reports. Prophylactic fluconazole in a dose of 3mg/kg every 72 hours was given if baby was less than 1000 grams and less than 28 weeks of gestation.

The indications for initiation of mechanical ventilation were (1) respiratory distress as assessed by Downes score ≥ 7 (2) apnoeic spells (3) oxygen saturation of < 88 % in preterms less than 34 weeks and < 94% for > 34 weeks gestation while receiving oxygen therapy (low flow oxygen at rates of 0.5-2 l/min by nasal prongs if < 2.5 kg and onto headbox oxygen if >2.5 kg) (4) blood gas pH <7.25. (5) Pa CO2 > 65 mm Hg (The unit did not have bubble CPAP machines during the study period).

Surfactant of bovine origin, porcine origin or BLES (Bovine Lung extract) was administered to babies with hyaline membrane disease (HMD) and meconium aspiration syndrome (MAS) in doses as recommended by the manufacturers. Surfactant was given as rescue therapy in babies > 30 weeks and prophylactically in those ≤30 weeks. Babies, whose oxygen requirement remained more than 60% after 24 hours of surfactant administration, received a second dose of the same brand of surfactant given earlier. The babies were ventilated with Takaoka ventilator (Atlanta and Carmel models). The initiation mode was time cycled pressure limited intermittent mandatory ventilation. The ventilation was weaned and the mode changed based on capillary blood gases and the clinical condition. All ventilated babies were sedated using midazolam or morphine injections and vecuronium was used for paralysis in babies requiring high mean airway pressures to maintain oxygenation. Extubation was attempted when the babies showed clinical improvement and reducing ventilator requirements (peak inspiratory pressure (PIP) of 16-18cm H2O, peak end expiratory pressure (PEEP) of 4 cm H2O, ventilator rate of ≤25 per minute, oxygen requirement of <40%). All babies were extubated onto low flow oxygen at rates of 0.5-1.5 l/min by nasal prongs if < 2.5 kg and onto headbox oxygen if >2.5 kg or in the presence of necrotising enterocolitis.

All details regarding ventilation parameters, the age at initiation of ventilation, age at extubation, duration of oxygen therapy, mode of delivery of oxygen, reventilation if needed, indication and duration of reventilation were recorded. Complications encountered during ventilation such as shock, sepsis, disseminated intravascular coagulation, pulmonary hemorrhage, primary pulmonary hypertension of newborn (PPHN), pneumonia, pneumothorax, patent ductus arteriosus, necrotising enterocolitis, their management, outcome and duration of hospital stay were recorded. To avoid a spuriously good outcome, 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 [11]. Chi-square test was used for categorical variables and Student's unpaired t test for continuous variables. P value <0.05 was considered significant for all the tests.

Results

There were a total of 2826 admissions to NICU during the study period (January 2008-December 2013). Out of 100 babies ventilated, there were 54 males and 46 female babies. An analysis of the mode of delivery showed that 74 were born by caesarean section, 24 by normal delivery and 2 by vacuum extraction. A majority of the babies were inborn (69 vs 31). Of the 100 neonates ventilated, 75

Table 1. *Mean gestational age and birth weight in relation to survival*

Parameter	Mean in survivors	Mean in expired	P value (SD)
Gestational age (weeks)	34.5 ± 3.5	32.4 ± 5.1	0.019 (4.07)
Birth weight (kg)	2.06 ± 0.79	1.62 ± 0.88	0.023 (0.833)

Table 2. *Profile of ventilated patients and relation to survival*

Parameter	Number	Percentage survival (%)
Gestational Age		
<28 weeks	7	14.3
28-30 weeks	12	66.7
31-32 weeks	14	71.4
33-34 weeks	20	95
35-36 weeks	19	78.9
37-40 weeks	25	80
>40 weeks	3	66.7
Birth Weight		
<1kg	6	33.3
1-1.49	31	61.3
1.5- 1.99 kg	18	88.9
2- 2.49 kg	19	94.7
>2.5 kg	26	76.9
Indications for Ventilation		
HMD	75	82.6
Sepsis	8	37.5
Asphyxia	7	100
MAS	6	50
CDH	2	0
Hydrops	1	0
PPHN	1	0
Downes Score		
≤ 6	15	53.3
≥ 7	85	78.8
Cord pH®		
<7.00	5	80
7.01-7.15	12	75
>7.15	61	84.6

®*Data available for only 78 neonates*

(75%) survived while 25 (25%) died. There were no significant gender differences in survival (p=0.487). A similar finding was observed with inborn and outborn babies.

A statistically significant difference was obtained between the mean gestational age of the survivors and those who expired. A similar result was seen with birth weight. ($p<0.05$) (Table 1).

The general profile of the study population and the survival outcome in relation to the various parameters are described in Table 2. Hyaline membrane disease was the commonest diagnosis followed by sepsis, asphyxia and meconium aspiration. The best outcome was observed in neonates ventilated for asphyxia (100%) followed by HMD (82.6%). The number who survived with a higher Downes score before ventilation was higher as compared to those with a lower score. Cord pH was available only in inborn babies and it was not found to be statistically significant. (Table 2)

Surfactant was given to 84 babies, of whom 74 had HMD, 6 had MAS and 4 with birth asphyxia. The one baby who did not receive surfactant in the HMD group expired.

An analysis of the ventilator parameters was made taking into consideration the age at which ventilation was initiated, duration of ventilation, age at extubation, initial and maximum ventilator settings. The maximum PEEP was higher and showed a trend towards significance (p=0.06) and the age (in hours) of initiation of ventilation was significantly later in those who expired (p=0.006). The maximum mean airway pressure (MAP), duration and age at ventilation though lower in those who survived but was not statistically significant. (Table 3)

During the course of ventilation, shock was the commonest complication which occurred in 84 babies with a survival of 73.8%. Other complications were sepsis, DIC, pulmonary hemorrhage, PPHN, pneumonia and pneumothorax. On applying multivariate logistic regression, DIC and pulmonary hemorrhage were found to be independently predictive of mortality. (Table 4). Two babies with HMD developed pneumothorax and both survived.

Table 3. *Comparison of ventilator parameters between survivors and expired*

Ventilatory parameter	Mean (Survivors) N-75	Mean (Expired) N-25	p value
Initial PIP (cm H2O)	22.27±3.19	22.27±3.19	0.56
Initial PEEP(cm H2O)	4.57±0.619	4.76±0.72	0.214
Initial FiO2	0.8633±0.1901	0.892±0.177	0.509
Initial MAP(cm H2O)	11.09±1.8	10.96±2.09	0.761
Maximum PIP(cm H2O)	23.6±3.4	24.28±4.6	0.43
Maximum PEEP(cm H2O)	4.7±0.63	5±0.76	0.06
Maximum FiO2	0.868±0.191	0.842±0.213	0.569
Maximum MAP(cm H2O)	11.9±1.9	12.01±1.99	0.585
Age at ventilation (hours)	9.13±14.3	46.25±113.45	0.006
Duration of ventilation (hours)	44.6±28.3	50.8±25.9	0.33
Age at extubation (hours)	52.09±27.7	59.24±29.2	0.274

Table 4. *Multivariate logistic regression for prediction of mortality*

Complications	Number with Complication	Survivors (%)	β coefficient	p Value
Shock	84	62 (73.8)	1.234	0.274
Sepsis	61	45 (73.7)	-1.323	0.591
DIC	19	7 (36.8)	2.154	0.009
Pulmonary Hemorrhage	10	1 (10)	2.902	0.019
PPHN	12	5 (41.6)	1.027	0.220
Pneumonia	7	5 (71.4)	0.442	0.629
Pneumothorax	2	2 (100)	-18.9	0.739
Constant			-2.4	0.021

P<0.05

Fourteen babies were reventilated out of which 5 babies expired. The causes of extubation failure were apnea of prematurity, sepsis, unresolved HMD, laryngeal edema, pneumonia, pulmonary hemorrhage and pneumothorax.

Discussion

In our series of 100 ventilated babies the commonest indication for ventilation was hyaline membrane disease. The other causes in order of decreasing frequency were sepsis, asphyxia and meconium aspiration syndrome. The overall survival was 75%, with the best outcome in asphyxia followed by HMD. The worst outcome was seen with congenital diaphragmatic hernia, hydrops and PPHN. Outcome was poor for babies with lower birth weight and lower gestational age

Hyaline membrane disease, as in our series, was the commonest indicaton for ventilation as in other studies from India in the past and a more recent series from China [2, 4, 6, 7, 13]. MAS was the commonest indication for ventilation in a study from South India [8].

Our survival statistics were similar to a large study from China (75.3%) [13]. In the previous studies from India, Saudi Arabia and Bangladesh the survival reported have ranged from 35-74% [2, 4-8, 12, 14]. In our series, 82.6% of the HMD group survived. The survival rate for HMD have ranged from 50- 65 in the other studies [1, 2, 4, 6-8, 12]. The better outcome could be because of the universal use of surfactant in all but one in the HMD group. But the outcome in babies <28 weeks was poor. Numerous trials from the developed world have proved that natural and synthetic surfactants reduced neonatal mortality and pulmonary air leaks. [16-19]. Sepsis had a survival of only 37.5% which is comparable to a few other studies [7, 20, 21]. Better prognosis was reported in other studies with survival rates ranging from 46.1-100 % [3, 4, 8, 13]. Those ventilated for asphyxia had the best outcome (100%). All these babies were ventilated at birth. Of the 7 babies with asphyxia 4 received surfactant because of surfactant deficiency diagnosed clinically and radiologically. The survival for those ventilated for asphyxia with a reported range of survival from 14% to 72.7% [4, 7, 8, 22, 23]. Meconium aspiration syndrome was the fourth common diagnosis in those ventilated with 50% mortality. All babies with MAS developed PPHN and were managed with inotropes and oral sildenafil. Various studies have reported varying survival rates ranging from no survivors [4, 7], to 60.7% in the series from JIPMER [8] and one study showing 100% survival [2].

The mean gestational age of the survivors was higher than those who expired. A similar finding was noted with birth weight, both of which were significant. These findings have been reported in the previous studies [4, 8, 12, 13, 21, 23]. Sepsis and pulmonary hemorrhage were the causes of death in babies less than 1 kg and those less than 28 weeks.

Paradoxically a subgroup analysis showed a progressively poor outcome with increasing gestational age [Table 2]. In the smaller gestation babies the most common diagnosis was HMD whereas in the higher gestational groups, MAS, pneumonia, hydrops, congenital diaphragmatic hernia and PPHN were present as secondary diagnosis in addition to respiratory failure, all of which had a reported poor outcome in many studies [4, 8, 12, 13].

Of the males, 77.8% survived as compared to 71.7% of the ventilated female babies which is similar to the study from China [13]. Females were found to have a better survival in other studies [8, 22].

The overall better survival rate seen in this retrospective analysis could probably because of the disease for which they were ventilated, namely HMD and the good response which was obtained with surfactant therapy.

In resource poor settings the Downes score is an excellent objective tool to assess the respiratory status objectively as it has been found to correlate with blood gases [24]. As 31% our babies were outborn, to provide uniformity we assessed the relationship between Downes score before initiating ventilation and outcome. Of those with a score ≥ 7, 78.7% survived as compared to 53.3% with a lower

score. This paradoxical response could be possibly because the Downes score correlates well with the severity of respiratory distress but has no bearing on the outcome of ventilated babies. Cord pH was available only in the 69 inborn babies and was not found to correlate with the mortality.

The initial and maximum ventilatory requirements were analyzed. Though maximum PIP, PEEP and MAP were higher in those who expired, this was not statistically significant. Mean Maximum PIP was higher in non survivors in other studies [8, 20]. There was no difference in the FiO2 requirements of the survivors and those who expired contrary to the findings in the two studies from India [8, 20].

Mean age at initiation of ventilation was significantly lower in the survivors. But we did not find any significance in the mean duration of ventilation and age at extubation though they were lower in the survivors. The mean length of ventilation was longer in the series from China [13].

The most frequent complication seen was shock in 84%. All of them required volume expansion and inotropes support of varying degrees. Sepsis was the next common complication. DIC and pulmonary hemorrhage were found to be independently predictive of poor outcome by logistic regression. Pulmonary hemorrhage occurred in 10 babies of whom 9 died. Of these 6 had HMD, 3 sepsis and 1 had PPHN. Pulmonary hemorrhage was a terminal event and developed 24 hours after surfactant administration in the HMD group. Other studies noted pulmonary hemorrhage after surfactant administration [4, 8]. Of the 12 babies with PPHN, 7 expired (58.3%). Babies with PPHN were managed with optimisation of ventilation, electrolytes, inotropes and sildenafil. The reported mortality in reports from the West where inhaled nitric oxide is used ranges from 10 % [26] to 57.9% [27]. Our unit does not have high frequency oscillator or facilities for nitric oxide therapy.

Two babies with HMD developed pneumothorax, both of whom survived. One developed pneumothorax while on ventilator and the other 24 hours after extubation. This is much less than that reported by other studies [5, 7, 8, 12, 13, 21, 28]. This could be partly explained by the unit policy of using paralysing agents during difficult ventilation or when lung compliance is poor.

Fourteen babies needed reventilation, of whom 5 died. Apnea, sepsis, laryngeal edema, pneumonia, unresolved HMD, pneumothorax and pulmonary hemorrhage were the reasons for reventilation. One baby with unresolved HMD received a second dose of surfactant and survived. Laryngeal edema was managed with a course of hydrocortisone and intubation with a smaller size endotracheal tube for 24 -48 hours.

Conclusions

In our study, the survival rate of ventilated babies was 75% and the commonest indication for ventilation was HMD. Among the factors analyzed, higher gestational age, birth weight and earlier age of initiation of ventilation was associated with a better outcome. Presence of DIC and pulmonary hemorrhage were predictive of poor outcome.

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