Original article

Clinical outcome of high frequency ventilation in neonates in neonatal intensive care unit

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Abstract

Background: Pulmonary disease is a major cause of mortality and morbidity in neonates. Some of them may require mechanical ventilation with high mean airway pressures to maintain adequate gas exchange. More unconventional modalities such as inverse ratio ventilation, high frequency ventilation or extracorporeal membrane oxygenation (ECMO) may be needed. **Objective**: To study the clinical outcome of neonates managed with HFV for past 5 years in Neonatal Intensive Care Unit (NICU). **Methods**: A retrospective study conducted at NICU from January 2007 to June 2013. All neonates who were managed with HFV were included in the study. **Result:** There were 39 neonates who were ventilated with HFV during that period. The survival rate was 20.5% (8 out of 39 subjects). 18 developed pulmonary hypertension, 5 of whom survived. Six (15.4%) presented with primary pulmonary hypertension (PHN) and 12 (30.8%) developed secondary PHN. In the survived group, 12.5% developed chronic lung disease and periventricular leukomalacia and in the expired group, 25.8% developed pulmonary haemorrhage. **Conclusions**: When HFV is instituted in infants who fail to show improvement with conventional ventilation, statistically significant improvement in arterial oxygen tension may occur without any change in oxygenation index. A longer period of conventional ventilation prior to HFV could be one of the factors that could interfere with the successful management with HFV.

Keywords: High frequency ventilation, neonates.

Introduction

Pulmonary disease is a major cause of mortality and morbidity in term and near term infants. Conventional mechanical ventilation (CMV) has been used for many years but this may lead to lung injury. Some of these infants may have such severe pulmonary disease as to require high mean airway pressures. More unconventional modalities such as inverse ratio ventilation, high frequency ventilation or extracorporeal membrane oxygenation (ECMO) may be needed in these infants.[1] Among these, high frequency oscillatory ventilation (HFOV) is a newer mode using lung protective strategy.[2] It is also a safer mode for use of higher mean airway pressure than that is generally used during CMV.[3] Studies suggest that HFOV is a better rescue therapy and also decreases the requirement of ECMO.[4,5]

The aim of this study was to evaluate the clinical outcome in neonates who were ventilated with high frequency ventilation (HFV).

Methodology

This was a retrospective study conducted at Neonatal Intensive Care Unit (NICU) at a referral hospital in South India from January 2007 to June 2013.The study protocol was approved by the institutional ethics committee. All neonates who were ventilated with High Frequency Ventilation (HFV) were included in the study. Drager Babylog 8000 plus with HFV option or SLE 5000 ventilator were used to provide HFV.

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In addition to demographic data such as gestational age, gender and birth weight, the date of birth, date of admission, whether born at our hospital or elsewhere, mode of delivery, the diagnosis and presence of primary and secondary persistent pulmonary hypertension (PPHN) were noted.

All neonates who had an indication for invasive ventilation received conventional ventilation initially. The oxygenation index (OI) was monitored and when it exceeded 25, HFV was commenced. The time of intubation (hours after delivery), mode used during conventional ventilation (CV) before the use of HFV, total hours ventilated in CV and HFV, total hours in CV after weaning from HFV were recorded. The use of surfactant and inhaled nitric oxide were also noted.

The ventilator settings on CV such as inspired oxygen concentration (FiO_2), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), respiratory rate (RR) and mean airway pressure (MAP) were noted. Similarly, settings of HFV such as FiO_2, amplitude, MAP and Hertz (Hz) were noted. The oxygenation index (OI) was calculated and recorded during both modes of ventilation. The arterial blood gas (ABG) analysis reports prior to the use of HFV and after the use of HFV in the 1st, 4th, 6th, 12th and 24th hours were noted.

The neonates who required reintubation and the hospital stay of all the neonates in the study group were recorded. The occurrence of complications such as chronic lung disease, periventricular leukomalacia, pulmonary haemorrhage, intraventricular haemorrhage, air leak syndrome, patent ductus arteriosus, retinopathy of prematurity, necrotising enterocolitis and hearing defects were also noted. The data were analysed to look for any differences between patients who survived and those who did not.

Statistical analysis

SPSS 16 was used for statistical analysis. Wilcoxon Signed Ranks Test was used to compare the OI values on conventional ventilation and HFV. Kaplan-Meier test was used in order to analyse the survival of the subjects.

Results

There were 41 neonates who were ventilated with HFV during the period January 2007 to June 2013 in NICU. Out of these, 2 neonates were discharged against medical advice and so were excluded from the statistical analysis. *Table 1* shows the baseline characteristics of remaining 39 neonates. *Table 2* shows the diagnosis of neonates included in the study. Among 39 subjects in the study, six (15.4%) presented with primary pulmonary hypertension (PPHN) and twelve (30.8%) developed secondary PHN. Thirteen (33.3%) of the 39 neonates received surfactant and eleven (28.2%) required inhaled nitric oxide therapy.

Table 1: Baseline characteristics of neonates requiring HFV

Baseline characteristics	Mean ±S.D.
Birth Weight (g) (mean ± S.D)	2261.67 ± 811.5
Gestational age in weeks (mean ± S.D)	35.49 ± 4.95
Mode of delivery NVD* n (%)	14 (35.9)
LSCS* n (%)	25 (64.1)

*NVD-normal vaginal delivery, LSCS- Lower Segment Caesarean Section.

Table 2: Diagnosis of neonates included in the study

Diagnosis	n (%)
Congenital diaphragmatic hernia	6 (15.4)
Meconium aspiration syndrome	6 (15.4)
Respiratory distress syndrome	18 (46.1)
Birth asphyxia	2 (5.1)
Congenital pneumonia	2 (5.1)
Pulmonary haemorrhage	1 (2.6)
Seizures	2 (5.1)
Congenital myopathy	1 (2.6)
Upper airway obstruction	1 (2.6)

Table 3 shows the time of intubation and duration of mechanical ventilation before HFV, on HFV, after HFV, total duration on ventilator and duration of NICU stay. All of the neonates were intubated within 48 h of life and received about 18.5 hours (median) of conventional ventilation before being managed with HFV.

Table 3: Time of intubation, duration of mechanical ventilation and NICU stay

Duration of support	Median [Interquartile range (IQR)]
Time to endotracheal intubation (h after birth)	1 (0-30)
Duration of mechanical ventilation before HFV (h)	18.5 (4-52.50)
Duration of HFV (h)	32 (11-83.25)
Duration of mechanical ventilation after HFV (h)	0 (0-30)
Total duration of mechanical ventilation (h)	74 (43.5-196.5)
Duration of NICU stay (h)	94.5 (43.5-204.75)

The parameters of conventional ventilation were recorded and analysed (*Table 4*). All the neonates required a FIO_2 of more than 90% and the mean airway pressure required was also higher.

Table 4: Settings on conventional ventilation (CV)

Settings on CV	Mean ± SD
Max FiO_2	0.92 ± 0.25
Max PEEP (cmH_2O)	5.24 ± 1.97
Max PIP (cmH_2O)	23.65 ± 6.35
Max RR (bpm)	42.68 ± 9.17

The HFV settings used are shown in *Table 5*. Oxygen requirement was more than 90% and mean airway pressure required was 15.87 cm H_2O (mean) to maintain adequate oxygenation. The median amplitude used was 62.46, with a frequency of 8.77 Hz.

Table 5: HFV settings of all neonates

Settings on HFV	Mean ± SD
Max FiO_2	0.93 ± 0.25
Max MAP (cmH_2O)	15.87 ± 3.61
Max Amplitude	62.46 ± 19.04
Max Hz	8.77 ±1.308

Table 6 shows the arterial blood gas values of the subjects on conventional ventilation and after 2 hours of initiating HFV. Among all the values, PaO_2 shows a statistically significant improvement after HFV.

Table 6: Arterial blood gas values and oxygenation index on conventional ventilation (CV) and after two hours of HFV

Parameter (Mean ± SD)	CV	HFV	p value
pH	7.14 ± 0.19	7.25 ± .29	0.238
PaO_2 (mm Hg)	42.91 ± 18.87	106.29 ± 101.37	0.007
$PaCO_2$ (mm Hg)	51.14 ±19.60	42.28 ± 18.56	0.079
HCO_3^- (mmol/L)	18.34 ± 7.05	18.70 ± 5.92	0.510
BE (mmol/L)	-8.07 ± 6.206	-8.08 ± 4.63	0.583
Oxygenation index	33.39 ± 18.188	31.79 ± 24.73	0.394

The survival rate was low at 20.5% (8 out of 39 subjects). Thirty one (79.5%) neonates died. Among the 39 subjects in the study, 18 developed pulmonary hypertension, 5 of whom survived. Six (15.4%) presented with primary pulmonary hypertension (PHN) and 12 (30.8%) developed secondary PHN. The mortality seemed higher in primary PHN with only one out of six surviving whereas 4 out of 12 who developed secondary pulmonary hypertension survived but the difference was not statistically significant.

Among the neonates that survived and expired, the duration of ventilation was analysed and is as shown in *Table 7*. The ventilation parameters between the survived and expired neonates were also analysed and are as shown in *Table 8*.

Table 7: Comparison of duration of ventilation and NICU stay between survived and expired patients [Median (interquartile range)]

Duration of Support	Survived	Expired
Time from birth to intubation (h)	0.5 (0,102)	4 (0, 30)
Duration of CV prior to HFV (h)	10 (4, 48)	20 (4, 66)
Duration of HFV (h)	48 (24, 105)	24 (7.5, 67)
Duration of CV after HFV (h)	48 (30, 115)	0 (0, 0)
Duration of mechanical ventilation (h)	196 (76, 201)	61 (20, 159)
NICU stay (h)	201 (93, 216)	72 (20,179)

Table 8: Comparison of ventilatory parameters used during conventional ventilation in the neonates who survived and those who expired.

Parameters	Survived	Expired	P value
FiO_2 (%)	71.43 ± 4.8	98.62 ± 0.74	0.000
PEEP (cmH_2O)	3.8 ± 2.6	5.54 ± 1.78	0.51
PIP (cmH_2O)	19.83 ± 10.32	24.5 ± 4.8	0.130
RR (breaths/min)	34 ± 17.42	45 ± 5.70	0.009
MAP (cmH_2O)	31.97 ± 19.5	32 ± 18.38	0.905

*FiO_2 - Fraction of inspired oxygen, PEEP- positive end expiratory pressure, PIP- Peak inspiratory pressure, RR- respiratory rate, MAP- mean airway pressure

Complications that occurred in these neonates were compared with survival *(Table 9)*.

Table 9: Distribution of complications in the survived and expired subjects

Complications	Survived n (%)	Expired n (%)	P value
Chronic Lung Disease	1 (12.5)	1 (3.2)	0.372
Pulmonary haemorrhage	nil	8 (25.8)	0.128
Intraventricular haemorrhage (Grade 4)	nil	1 (3.2)	0.795
Air Leak Syndrome	nil	2 (6.5)	0.628
Periventricular leukomalacia	1 (12.5)	1(3.2)	0.372
Patent Ductus Arteriosus	Nil	Nil	Nil
Necrotising Enterocolitis	Nil	1 (3.2)	0.795
Retinopathy of Prematurity	Nil	Nil	Nil
Hearing Defect	Nil	Nil	Nil

The Kaplan Meir survival analysis in the study showed that the chance of survival was better in neonates with no PPHN when compared with primary and secondary PPHN, even when supported with HFV (*Figure 1*).

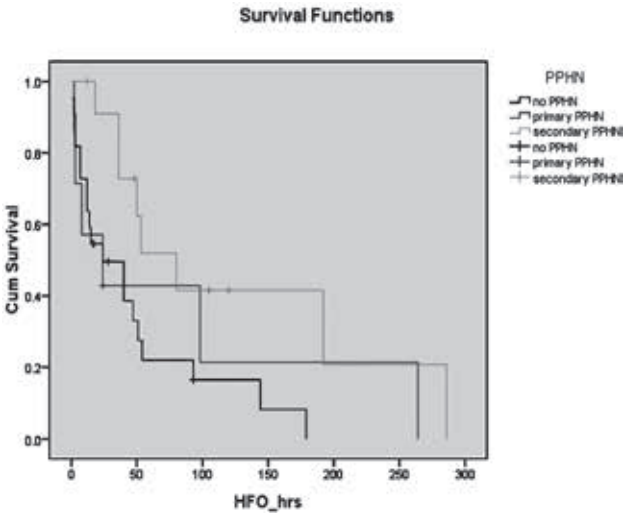

Figure 1: Kaplan Meir survival analysis in relation to PPHN and hours of HFV.

Discussion

High frequency ventilation was received with great enthusiasm when it was first introduced but, unfortunately, several randomised trials have provided mixed results with regard to pulmonary outcomes.[6] High frequency ventilation (HFV) has been compared with conventional mechanical ventilation (CMV) since the 1980s. The HFV has been extensively investigated in premature neonates with infant respiratory distress syndrome, a population specifically at risk for chronic lung disease (CLD). Unfortunately, the results of these studies were equivocal.[7,8] Pooled estimates of pulmonary outcomes failed to show clinically relevant differences among HFV and CMV.[9]

In this study, all neonates ventilated with HFV were enrolled. HFV was used in those neonates when conventional ventilation failed to improve the clinical condition.

The results of a linear meta-analysis conducted in 2007 showed that a longer time on CMV prior to initiation of HFV, higher gestational age and birth weight seemed to be positively associated with a relatively better outcome in HFV.[10] In our series, of 39 neonates, there was no difference in the hours of ventilation with CV before HFV in the survived and expired group. The same meta-analysis also showed a clear trend of decreasing differences in pulmonary outcome between HFV and CMV in randomised trials conducted in premature neonates with RDS over the years. Whether elective HFV or avoiding CMV prior to initiating HFV would be useful in treating RDS in subgroups of more premature infants and neonates with a higher risk of CLD was not clear from this meta-analysis. Our study showed significant improvement in PaO_2 after HFV

when compared to CV and but the improvement in oxygenation index was not statistically significant.

In the largest trial of HFV versus CMV to date, Johnson and colleagues[11] included 797 preterm infants and used different types of HFOV in the HFV arm. This trial demonstrated no difference in air leaks, or death in the HFV-treated group compared with the CMV-treated group. Our study showed that there was a high incidence of complications in these neonates. In the survived group, 12.5% developed chronic lung disease and periventricular leukomalacia. In the expired group, 25.8% developed pulmonary haemorrhage which is quite high when compared to other complications.

Conclusions

When HFV is instituted in infants who fail to show improvement with conventional ventilation, statistically significant improvement in arterial oxygen tension may occur without any change in oxygenation index. There is a high incidence of complications and high mortality rate in these neonates. A longer period of conventional ventilation prior to HFV could be one of the factors that could interfere with the successful management with HFV. Further studies can focus on the time of commencement and protocols for weaning of HFV and further management in this group of high risk neonates.

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