RESEARCH BRIEF

High Frequency Oscillatory Ventilation *versus* Synchronized Intermittent Mandatory Ventilation in Preterm Neonates with Hyaline Membrane Disease: *A Randomized Controlled Trial*

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This randomized controlled study was conducted to compare the efficacy and safety of High frequency oscillatory ventilation (HFOV) and Synchronized intermittent mandatory ventilation (SIMV) in preterm neonates with hyaline membrane disease requiring ventilation. The ventilation strategy in both the groups included achieving optimal lung recruitment and targeted blood gases. 49 patients received HFOV and 61 SIMV. The baseline characteristics were similar in both the groups. HFOV group demonstrated better early oxygenation, enabled reduction in oxygenation index (OI) within 24 h of ventilation (difference in mean OI at 1, 6, & 24 h of ventilation: *P*=0.004 in HFOV, and 0.271 in SIMV group). Duration of hospital stay was shorter in HFOV group (*P*=0.003). The complication rate and survival were similar in two groups.

Key words: *Complications, Hyaline membrane disease, Outcome, Neonates, Preterm, Ventilation.*

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Hyaline membrane disease (HMD) is the commonest condition requiring ventilation in preterm neonates. Although, conventional ventilation or Synchronized intermittent mandatory ventilation (SIMV) with lung protective strategy reduces the complication and improves outcome, it may still cause mechanical injury to the lungs [1-3]. High frequency oscillatory ventilation (HFOV), a technique of rapid ventilation with use of very small tidal volume has potential of reducing ventilator associated lung injuries [4,5], particularly when started early, before significant lung damage has been caused by tidal ventilation [6]. However, utility of HFOV in ventilatory management of HMD remains controversial [7,8].

HFOV as a modality of neonatal ventilation has been infrequently reported from India [9, 10]. This study was done with the objective of comparing HFOV with SIMV as primary mode of ventilation in preterm infants with HMD.

METHODS

This randomized, controlled study was conducted at our level III neonatal unit from October 2007 to November 2010 in preterm neonates having HMD [11]. The criteria of initiation of ventilation was any of the followings (*i*) PaO_2 <50mmHg or SpO_2 <88% on FiO_2 ≥0.8, (*ii*) $PaCO_2$ >60 mmHg with pH <7.25, (*iii*) failure of optimal CPAP (>9 cm of water) or apnea on CPAP. Babies with birthweight <750 g, major congenital anomaly, perinatal asphyxia, shock (mean blood pressure <2 SD from mean for weight despite 20µg /kg body weight/min of dopamine/dobutamine, alone or combined), and prior air leak were excluded. Patients who did not complete initial 24 hr of ventilation were excluded from analysis. The study was approved by the Institutional ethical committee and written informed consent was obtained. Eligible infants were randomly allocated to receive either HFOV using Drager Baby log 8000 plus or SIMV using SLE 2000. The random allocation sequence was generated by doing simple randomization using a web-based random number generator [12], and slip of paper bearing the intervention was kept in serially numbered, opaque, sealed envelopes. Statistician generated the allocation sequence and senior resident allocated the groups by opening the serially numbered envelope once the patient was found eligible for initiating mechanical ventilation and had given consent.

Strategy for ventilation in both the groups emphasized lung recruitment to ensure adequate lung inflation (8 to 9 posterior ribs, at level of the top of right hemidiaphragm on chest *X*-ray). Bedside chest *X*-ray was taken with baby still being connected to the ventilator, initially within one hour of initiation of ventilation and subsequently as and when required. Target values for PaO_2, $PaCO_2$ and SpO_2 were 55-80 mmHg, 40-55 mmHg and 89-95%, respectively. HFOV was begun at a mean airway pressure (MAP) of 10-12 cm of water, frequency 10-12 Hz and FiO_2 0.3-0.5 (irrespective of pre-ventilation FiO_2). I/E ratio were automatically set.

Amplitude was increased until the infant's chest was seen to be vibrating. Ventilator settings were adjusted to meet the target blood gas values and lung inflation. Oxygenation was managed by adjustment of MAP and the FiO_2. $PaCO_2$ was managed by adjustment of the oscillatory amplitude, and occassionally, frequency. In situation of air leak, the strategy was to change to low volume and high FiO_2 with the reduction in MAP. SIMV was started with positive end expiratory pressure (PEEP) at 5-7 cm of water depending on the FiO_2 and lung inflation, and peak inspiratory pressure (PIP) of 16-18, sufficient to cause visible chest inflation. Inspiratory time (Ti) of 0.35-0.45 was allowed, with rate of 40 breaths per min to a maximum of 60. It was aimed to keep lower tidal volumes by using lower PIP and optimal PEEP to maximally recruit lungs. Subsequently, ventilation settings were adjusted to meet target saturation and blood gases. Surfactant was used as soon as possible.

The protocol for both HFOV and SIMV included aggressive criteria for weaning ventilatory support and extubating infants. During weaning from HFOV, priority was given to reduce FiO_2 to 40-50% before weaning MAP (except where over inflation was evident). MAP was decreased by 1-2 cm H_2O at one time and the effect was judged 15-20 min after the change. Amplitude was decreased to 30-50% as tolerated and frequency was weaned last. Similarly for SIMV, priority was given to wean FiO_2 to 40-50% and to reduce PIP as lung compliance improves, based on observed chest movement, degree of aeration on chest radiograph and $PaCO_2$ levels. Patients were extubated as soon as they were stable for 6-12 hours on minimal ventilatory support, with an $FiO_2 \leq 0.35$, Ti =0.35, PIP ≤15, PEEP ≤4, RR ≤15 on SIMV; and $FiO_2 \leq 0.35$, MAP of ≤7 cm H_2O and amplitude <40% on HFOV. Infants <1500 g were treated with aminophylline

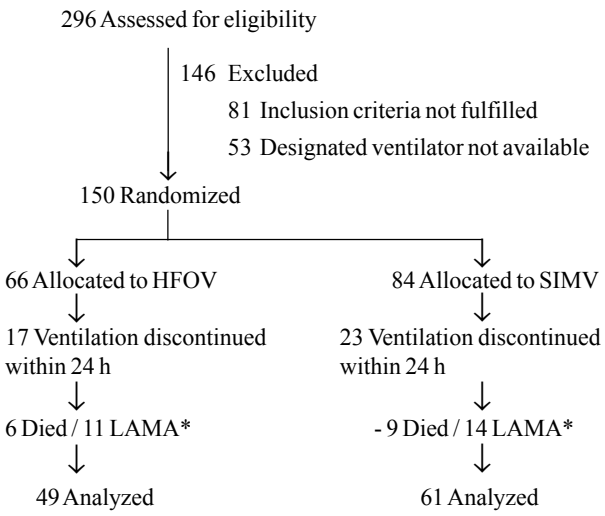

FIG. 1 *Flow diagram of patient enrolled*
*LAMA= left against medical advice

before extubation. All infants whether on HFOV or SIMV were placed on nasal CPAP after extubation and then subsequently shifted to O_2 hood. Other supportive care was provided to all patients as per unit protocol. Patients were discharged once they were stable without O_2 requirement for at least 72 hrs, complications managed, and on full oral feeds.

Outcome parameters observed were FiO_2, MAP and oxygen index (OI) at 1, 6 and 24 hr of ventilation; duration of ventilation and hospital stay; oxygen requirement beyond day 28; survival; and complications. Standard definitions were followed for defining complications [11, 13, 14].

Accepting α error of 0.10 (two sided) and β of 0.20 (80% power), a sample size of 49 in each group was calculated to detect a medium difference (standardized effect size 50%) in the two groups for the primary outcome, oxygen index [15]. However, it was decided to recruit and randomize 150 subjects, considering that ventilation in some patients in either group will be discontinued in the initial 24 hours. Categorical variables were compared by using chi square or Fisher exact test. Continuous variables were compared by student t-test, Mann Whitney U test or ANOVA test (serial measurements).

RESULTS

A total of 150 patients were enrolled, of 296 assessed for eligibility ***(Fig.* 1)**. One hundred and twenty two infants had received a trial of CPAP before going on to mechanical ventilation, either HFOV or SIMV, and 28 were directly put on mechanical ventilator.

The baseline characteristics of patients including age at initiation of ventilation and age at delivery of surfactant were similar in both the groups (***Table* I)**. The FiO_2, MAP and OI at 1 hour of ventilation were comparable in both the groups. There was significant difference with decline in mean FiO_2 (P=0.000), MAP (P=0.003) and OI (P=0.004), measured at 1 hr, 6 hr and 24 hr, respectively on first day of ventilation in HFOV group. However, in SIMV group, the difference in these parameters at various study points was not significant (***Table* II**).

Mean PaO_2 at 1 hr, 6 hr, and 24 hr in HFOV group was higher than those with SIMV, with insignificant difference in mean MAP at corresponding time point but with higher mean FiO2 (at 6 and 24 hour) in SIMV group **(*Table* II)**. This difference in mean PaO_2 was significant at 1 hour (P=0.001) and 6 hour (P<0.001) only. Mean $PaCO_2$ in HFOV and SIMV group was not significantly different.

DISCUSSION

We used lung recruitment strategy in both the groups and there was no switchover from HFOV to SIMV or vice-versa. Different ventilation strategies have been used in various studies where HFOV was compared with CV for

WHAT THIS STUDY ADDS?

- High frequency oscillatory ventilation was associated with better early oxygenation and shorter hospital stay compared to synchronized intermittent mandatory ventilation in preterm neonates with hyaline membrane disease.

ventilation in preterms, responsible for conflicting results [8]. Courtney, *et al*. [16] had also used similar ventilation policy as of ours. However, in another large trial most of the patients were switched from HFOV to CV for weaning and also more than one high frequency ventilators were used [17].

HFOV patients in the present study demonstrated higher mean PaO_2 compared to SIMV at various points of measurement, at comparable MAP and lower FiO2, reflecting better gas exchange with HFOV. Remarkably, FiO_2 could be weaned earlier in patients on HFOV. Improved oxygenation (lower FiO_2 requirement) and lower $PaCO_2$ within 24 hr of randomization and reduced incidence of new air leaks have been demonstrated in multicentric trial using HFOV with lung recruitment strategy in infants with severe RDS, but the mean airway pressure used in HFOV group was higher than CMV [18]. Gerstmann, *et al*. [19] have reported rapid oxygenation improvement and less frequent surfactant redosing in surfactant treated preterms with RDS receiving HFOV, compared to CV. Survival rate was lower in surfactant delivered patients receiving SIMV than those with HFOV in our study, probably because of higher incidence of pulmonary haemorrhage in SIMV patients.

TABLE I BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	*HFOV (n=49)*	*SIMV (n=61)*
Birthweight (g), mean ±SD	1398± 321	1393±320
Gestation (wks), mean ±SD	32.0±2.4	31.9±2.5
Male : Female	29:20	37:24
Outborn : Inborn	31:18	46:15
Vaginal delivery	32 (65.3%)	36 (59.0%)
LSCS delivery	17 (34.7%)	25 (41.0%)
Maternal complication		
APH	4 (8.2%)	9 (14.8%)
PET	2 (4.1%)	5 (8.2%)
Multiple pregnancies	2 (4.1%)	3 (4.9%)
PROM	9 (18.4%)	14 (23.0%)
Antenatal steroid*		
Complete	17 (34.7%)	31 (50.8%)
Incomplete	6 (12.2%)	7 (11.5%)
Surfactant given	21 (42.9%)	25 (41.0%)
Age at surfactant received (hr)#	14 (10-24%)	13 (12-31%)
Positive blood culture*	11 (22.4%)	8 (13.1%)
Age at start of ventilation (hr)	5 (4-14%)	4 (2-19%)

*Figures in parentheses depict % unless specified, *Betamethasone: complete- 2 doses given >24 hrs but no more than 7 days before delivery, incomplete- any dose given <24 hrs or >7 days before delivery, PET=Pre-eclamptic toxemia, APH=Ante partum hemorrhage, PROM=Prolonged rupture of membrane (>18 hr); at initial work up; #Median (IQR).*

In the present study, total hospital stay was longer in SIMV than HFOV group. Possibly more lung injury and higher incidence of ventilator associated pneumonia, PDA and longer requirement of supplemental oxygen, though insignificantly, in SIMV group might have contributed to longer hospital stay of patients in this group. There was no significant difference in survival, days of ventilation and oxygen requirement beyond day 28 in the two groups, similar to study by Johnson, *et al*. [17]. However, Courtney, *et al*. [16] have reported shorter duration of ventilation and lesser incidence of CLD in HFOV group. The incidence of CLD was much less in our study than other studies [16, 17], because infants in present study were more mature and required ventilation for shorter duration.

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TABLE II OUTCOME AND ABNORMAL BLOOD GAS PARAMETERS

Parameter	*HFOV (n=49)*	*SIMV (n=61)*	*P value*	*Mean difference (95% CI)*
At 1 hr*				
FiO_2 (%)	61.8± 11.8	66.1±13.4	0.087	-4.2 (-9.1 to 0.6)
MAP (cm H_2O)	11.21±1.3	10.8±2.1	0.283	0.4 (-0.3 to 1.1)
OI	10.2± 3.6	11.5±4.8	0.107	-1.3 (-3.0 to 0.3)
At 6 hr*				
FiO_2 (%)	54.7±13.5	66.1±15.5	0.000	-11.4 (-17.0 to -5.9)
MAP (cm H_2O)	10.8±1.8	11.0±1.9	0.502	-0.2 (-0.9 to 0.5)
OI	8.5±3.8	11.4±4.7	0.000	-3.0 (-4.6 to -1.3)
At 24 hr*				
FiO_2 (%)	48.2±14.7	61.2±14.7	0.000	-13.1 (-18.7 to -7.5)
MAP (cm. H_2O)	10.0 ±1.8	10.5±2.1	0.157	-0.5(-1.3 to 0.2)
OI	7.5±4.4	10.3±4.6	0.002	-2.8 (-4.5 to -1.1)
Duration of ventilation (hr)*	67.3±33.1	131±183.4	0.284	-63.6(-111 to -15.8)
O_2 beyond Day 28	1(2%)	4(6.6%)	0.379	
Hospital stay (hr); Mean (SD)	247(171)	404(401)	0.003	158(-270 to -44)
Survival	34 (69.4%)	41 (67.2%)	0.808	
Extubation failure†	5 (10.2%)	7 (11.5%)	0.832	
Complication				
VAP	6 (12.2%)	13 (21.3%)	0.211	
IVH	4 (8.2%)	4 (6.6%)	1.000	
PDA	4 (8.2%)	7 (11.5%)	0.752	
ROP	2 (4.1%)	4 (6.6%)	0.690	
PH	6 (12.2%)	9 (14.8%)	0.703	
PVL	1 (2.0%)	1 (1.8%)	1.000	
Abnormal ABG (at 1hr /6hr/ 24 hr)*				
PaO_2 <50 mmHg	2 (4.1%)	5 (8.2%)	0.458	
PaO_2 >90 mmHg	6 (12.2%)	2 (3.3%)	0.136	
$PaCO_2$<35 mmHg (PH>7.45)	16 (32.7%)	9 (14.8%)	0.026	
$PaCO_2$>60 mmHg (PH<7.3)	2 (4.1%)	8 (13.1%)	0.180	

*†Need for reintubation within 24 hr of extubation, VAP= Ventilator associated pneumonia, IVH= Intraventricular haemorrhage, PDA= Patent ductus arteriosus, ROP= Retinopathy of prematurity, PH= Pulmonary haemorrhage, PVL= Periventricular leucomalacia; #Number of episodes; *Mean±SD.*

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