Randomised Controlled Trial Of Low (4-5mL/Kg) Vs. High (7-8 mL/Kg) Tidal Volume Using Volume Guarantee Ventilation – A Pilot Study

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Introduction

- Very Low Birth Weight Infants (<1500 grams) are born with surfactant deficiency and many require invasive mechanical support.
- Volume targeting appears to be a better modality than pressure targeting.
- Since volume guarantee (VG) helps to provide a more precise tidal volume, the debate has now shifted to what the ideal tidal volume should be.
- The recommended tidal volume varies from 4-8 mL/kg, but the optimal tidal volume has yet to be determined.
- To date, no study has addressed a comparison of "low" (4-5 mL/kg) versus "high" tidal volume (7-8 mL/kg) in premature infants with respiratory distress syndrome (RDS).

Aims and Objectives

To compare a lower (4-5 mL/kg) to a higher (7-8 mL/kg) tidal volume during volume guarantee ventilation of preterm infants with RDS.

Methodology

- This randomised trial was conducted at North Tees Hospital from 2013-2016.
- Inclusion criteria:
 - Preterm newborns <32 weeks' gestation or <1500 grams birthweight with RDS, who required mechanical ventilation within 12 hours of birth
- Exclusion criteria
 - Serious congenital anomalies
 - Congenital diaphragmatic hernia
 - Cyanotic congenital heart disease
 - Airway anomalies
 - Abdominal wall defects
 - Ventilation initiated prior to transfer from other centres
- Subjects were randomised to receive lower (4-5 mL/kg) or higher (7-8 mL/kg) tidal volume using VG. The dead space was standardized by using prescribed trimming of the external portion of the endotracheal tube.
- All subjects received surfactant and were managed by a strict protocol (Figure 1) with allowed rescue by high frequency ventilation for defined criteria.
- The primary outcome was the time to achieve a 25% reduction from the initial peak inspiratory pressure (PIP).
- Secondary outcomes included the duration of mechanical ventilation, and common respiratory and non-respiratory complications.
- Time-sensitive variables were analysed using survival statistics (Kaplan-Meier and log rank test). Categorical variables were analysed by Chi-square and continuous variables by independent t-test; non-parametric parameters were assessed by the Wilcoxon rank sum test. Linear analysis was performed by Cox regression, and significant variables underwent multivariate analysis. The analyses were performed using SPSS® version 20.0.

Figure 1: Protocol

Results

Figure 2: CONSORT Flow Diagram

Table 1: Demographic Data and Disease Severity at Baseline

Parameter	Higher V _t (n=58)	Lower V _t (n=58)	P
Male/Female	20/14	22/14	0.33
Antenatal steroids, two doses	24 (70.6%)	22 (65.1%)	0.259
Cesarean delivery	15 (44.36%)	13 (36.1%)	0.52
Birthweight, grams, mean (SD)	1064.55 (193.56)	1025.42 (270.88)	0.63
Gestational age in weeks, median (IQR)	27.29 (23.14-31.57)	27.43 (23.57-31.00)	0.995
Age at initial intubation in minutes, mean (SD)	32.7 (23.2)	25.6 (70.1)	0.76
PiO ₂ on admission, mean (SD)	0.35 (0.18)	0.37 (0.23)	0.7
Oxygenation index on admission, mean (SD)	7 (5.44)	4.5 (3.3)	0.02
Respiratory rate, mean (SD)	54.7 (14.9)	60.2 (15.1)	0.13
Initial pCO ₂ mmHg, mean (SD)	33 (15.7)	40.9 (12.7)	0.03
Minute volume, mL/kg/min, mean (SD)	35.3 (13.2)	289 (90)	0.02
Dynamic Compliance, mL/cm H ₂ O/kg, mean (SD)	0.37 (0.27)	0.5 (0.34)	0.10

FiO₂ - Fractional inspiratory oxygen; pCO₂ - Partial pressure of carbon dioxide;

- There were 97 eligible infants; 70 were randomised (Figure 2)
- High and Low groups were similar in their demographic profiles (Table 1)
- The primary outcome, time to reduce PIP by 25% (median [IQR]), was 13.6 [8.8 - 25.2] hours and 17.4 [7.7 - 27.8] hours, respectively, for higher and lower tidal volumes (p=0.678). (Table 2, Figure 3)
- The total duration of mechanical ventilation (median [IQR]) for higher vs lower tidal volume was 33.3 (22-368.8) and 61.8 (15.4-177.5) hours, respectively (p=0.959). (Table 2, Figure 4)
- Though tidal volume and PIP were different between groups, minute volume and pCO₂ were not. (Table 3, Figure 5)
- There were no differences between the groups for respiratory and non-respiratory complications. (Table 2, Figure 6)

Table 3: Ventilatory parameters

Parameter	High V _t	Low V _t	P value
Mean (CI) TV mL/kg	6.06 (5.5-6.62)	4.4 (3.92-4.88)	0.000028
Mean (CI) MV mL/kg/min	291.1788 (255.49 - 326.85)	252.4042 (216.32-288.48)	0.132
Mean (CI) PIP cm H ₂ O	26.2744 (24.59 - 27.95)	18.8 (16.19 - 21.43)	0.000012
aCO ₂ (CI) mmHg	34.1 (29.3-38.9)	38.7 (34.1-43.4)	0.174

V_t - Tidal Volume; MV - Minute Volume; PIP - Peak inspiratory pressure; aCO₂ - Arterial CO₂

Figure 5: Ventilatory parameters

Primary and Secondary Outcomes

Table 2: Comparison of Primary and Secondary Outcomes

Parameter	Higher V _t	Lower V _t	P
25% reduction in PIP, hours, median (IQR)	13.6 (8.8-25.2)	17.4 (7.7-27.8)	0.678
Duration of mechanical ventilation, hours, median (IQR)	33.3 (22-368.8)	61.8 (15.4-177.5)	0.959
Air leak events	3 (9%)	1 (3%)	0.350
PDA requiring medical treatment	9 (26.4%)	7 (19.4%)	0.574
PVL	2 (5.9%)	6 (16.7%)	0.438
NEC, Bell stage II or greater	4 (11.8%)	8 (22.2%)	0.667
ROP - Stage 3	7 (20.6%)	5 (13.9%)	0.445
BPD at 36 PMA	20 (58.8%)	16 (44.4%)	0.368
Survived to discharge without CLD	11 (32%)	13 (36%)	0.804

PDA - Patent Ductus Arteriosus; PVL - Periventricular leukomalacia; NEC - Necrotising enterocolitis; ROP - Retinopathy of prematurity; BPD - Bronchopulmonary Dysplasia

Figure 3: Primary outcome

Figure 4: Total duration of mechanical ventilation

Figure 6: Pulmonary and non-pulmonary complications

Summary and Conclusions

Figure 7

- This small pilot trial failed to demonstrate differences attributable to lower or higher tidal volume delivery in a small population of infants with RDS managed with volume guarantee ventilation.
- It is possible that both tidal volume ranges selected for study are near the functional residual capacity and that larger differences might be necessary to show a change. (Figure 7)