Volume-guaranteed Ventilation Versus Pressure-controlled Ventilation in Preterm Infants with Respiratory Distress Syndrome: A Randomized Controlled Trial

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ABSTRACT

Background: This study was targeted toward comparing volume-guaranteed (VG) ventilation with conventional pressure-controlled (PC) ventilation in preterm infants with respiratory distress syndrome (RDS) in terms of the facilitation of weaning and extubation and occurrence of complications, such as pneumothorax, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC).

Methods: This single-center randomized controlled trial was conducted on neonates who were mechanically ventilated in the Neonatal Intensive Care Unit of Kasturba Hospital Manipal Udupi, Karnataka, India. Infants with the gestational age (GA) of 27-34 weeks with RDS requiring mechanical ventilation in the first week of life were randomized to receive either SIMV-PC or SIMV-VG ventilation. Infants were stratified into two GA groups of 27-30 and 31-34 weeks. Sealed opaque envelope was used to randomize the infants into two treatment modalities. Sample size was calculated as 120 and 60 in each treatment group.

Results: A total of 115 neonates were enrolled. The mean GA and birth weight of the treatment groups were 31±2.3 weeks and 1230±374 g, respectively, and 70% of them received antenatal steroids. As the primary outcome variable, the total duration of ventilation was 8 h (range: 3-17) (median and IQR) in the SIMV-PC group and 6 h (range: 3-13) in the SIMV-VG group (P=0.366). Stratified analysis of neonates with the GA of > 31-34 weeks showed a significant difference between the VG and PC ventilation groups regarding the duration of ventilation.

Conclusion: There was a decrease in the duration of ventilation in VG ventilation, compared to that in PC ventilation at a higher GA. The leak was the major issue with VG ventilation in the lower GA group.

Keywords: RDS, SIMV-PC, SIMV-VG

Introduction

Mechanical ventilation still has remained as the mainstay of management in newborns with respiratory distress syndrome (RDS)(1). However, over the years various studies have shown that ventilation itself causes lung injuries, such as barotrauma, volutrauma, atelectotrauma, and biotrauma. These problems may further lead to long-term complications, namely bronchopulmonary dysplasia (BPD).

In order to reduce such ventilation-induced lung injuries, modern neonatal ventilators have volume-guaranteed (VG) modes alternative to traditional pressure-controlled ventilation (PCV).

The new technology aims to deliver a more stable tidal volume in the face of changing compliance and resistance. Therefore, a more stable partial pressure of carbon dioxide (PaCO₂) is produced with reduced frequency of hypercarbia or hypocarbia. The VG mode also facilitates automatic weaning and as the patient lung compliance improves, the peak inspiratory pressure is automatically reduced to attain the set tidal volume (1-3).

However, the major challenge of any dual-control mode of ventilation, such as VG is interference of leak, which may either trigger as
assisted breath or cause dyssynchrony. Leak problem is much more common in infants than adults because of using uncuffed tubes. As a result, success of the VG ventilation in infants, especially extreme preterm newborns depends upon the amount of present leak.

With this background in mind, the main aim of this study was to compare the VG ventilation with the traditional PCV in terms of mechanical ventilation duration, as well as the associated neonatal morbidity and mortality.

Methods
This single-center randomized controlled trial was conducted in level III neonatal intensive care unit (NICU) in Kasturba hospital, a tertiary care center, Manipal, Udupi, India. All the preterm neonates of the gestational age of 27-34 weeks, ventilated within the first week of life for RDS were enrolled in the study.

Stratified block randomization technique was applied and the infants were stratified into the two strata of 27-30 and 31-34 weeks gestational age. The sealed opaque envelope was used to allocate the subjects into the two treatment groups. All the infants were enrolled in the study with informed consents of the parents. The study was approved by the Institutional Ethics Committee (IEC) with the code of IEC Reg No: ECR/146/Inst/KA/2013CTRI No: REF/2016/03/011042.

The inclusion criteria entailed being preterm neonate, having gestational age of 27-34 weeks, and being ventilated for RDS within the first week of life. The neonates with congenital cyanotic heart diseases, major congenital malformations, air leak syndromes, and need for high-frequency oscillatory ventilation (HFOV) at admission were excluded from the study. All the infants were ventilated by Dragger Babylon 8000 and 8000 plus ventilators (made in Germany). The study was performed during March 2016-July 2017. The ventilation modes provided by VG and PCV were SIMV-VG and SIMV-PC, respectively.

The sample size for the present study was calculated as 120 based on the formula and the participants were divided into two groups of 60. All the data were analyzed by Mann-Whitney U test for the continuous variables and Chi-square test for the categorical variables using the SPSS software version 19.

The initial settings for the subjects on VG included TV, PEEP, Ti, respiratory rate (RR), flow rate, and fraction of inspired oxygen (FiO2) of 5 ml/kg, 4-6 cmH2O, 0.35-0.45 sec, 35-45 bpm, and 5-7 L/min, and 21-100%, respectively. In the PCV group, the initial settings were PIP of 14-18 cmH2O, PEEP of 4-6 cmH2O, Ti of 0.35-0.45 sec, respiratory rate of 35-45 bpm, flow rate of 5-7 L/min, and FiO2 of 21-100%.

The neonates of the PCV group were extubated when the PIP, FiO2, PEEP and RR reached ≤ 14 cmH2O, ≤ 0.3, 4-5 cmH2O, and ≤30 bpm. Moreover, extubation in the VG group was executed once FiO2, PEEP, and RR reached ≤ 0.3, 4-5 cmH2O, and ≤30 bpm. Once the extubation criteria were met, methylxanthines either aminophylline or caffeine were administered according to the NICU protocol as 5mg/kg and 20 mg/kg bolus, respectively. Afterwards, the neonates were extubated.

The criteria considered as failure included: 1) need for higher MAP of greater than 15 cmH2O, 2) Oxygenation Index (OI) of >15 for three consecutive hours, 3) crossover to either treatment modes or high-frequency ventilation (HFV), and 4) Need for scaling up the ventilation strategy with HFV of the inhaled nitric oxide upon the physician decision.

The primary outcome of the study was the total duration of mechanical ventilation, which was compared between the two groups. In addition, we assessed the incidence of the complications, such as air leaks, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and periventricular leukomalacia (PVL).

Results
Figure 1 represents the CONSORT Flow. A total of 115 infants were enrolled in the study with the mean gestational age of 31±2.3 weeks and birth weight mean of 1219±374 g. The infants were allocated to the two groups as 58 in the PCV and 57 in the VG groups. Table 1 shows the demographic characteristics of both groups. The total duration of ventilation as the primary outcome variable was compared between the two treatment groups of 27-30 weeks gestational age strata. The result showed that median duration of the requirement in the infants of the PCV group was 8 h (5-12, IQR) and in the VG group was 7 h (5-15) (P=0.74).

When this variable was compared in the strata of 31-34 weeks gestational age, the median duration for the infants in the PCV group was 10 h (5-14, IQR) and in the VG group was 5 h (2-12). The statistical analysis demonstrated a significant difference between the two groups (P=0.039). Post-extubation, the CPAP was used as the primary mode of non-invasive ventilation in both treatment groups. Table 3 depicts comparison of
**Table 1.** Demographic characteristics of the infants in the PLV and VTV groups

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>PLV (n=58)</th>
<th>VTV (n=57)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (mean±SD)</td>
<td>30±2.32</td>
<td>30±2.25</td>
<td>0.97</td>
</tr>
<tr>
<td>Birth Weight (mean±SD)</td>
<td>1203±409</td>
<td>1236±338</td>
<td>0.33</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/21</td>
<td>24/16</td>
<td>0.31</td>
</tr>
<tr>
<td>Antenatal steroids n (%)</td>
<td>30 (73%)</td>
<td>27 (67%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Caesarean delivery n (%)</td>
<td>32 (78%)</td>
<td>34 (85%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Surfactant administration n (%)</td>
<td>34 (83%)</td>
<td>37 (92%)</td>
<td>0.19</td>
</tr>
<tr>
<td>One-minute Apgar score (Median)</td>
<td>8</td>
<td>7</td>
<td>0.53</td>
</tr>
<tr>
<td>Five-minute Apgar score (Median)</td>
<td>9</td>
<td>9</td>
<td>0.41</td>
</tr>
<tr>
<td>Methylxanthines n (%)</td>
<td>30 (73%)</td>
<td>26 (65%)</td>
<td>0.644</td>
</tr>
</tbody>
</table>

**Table 2.** Comparison of PLV with VTV in terms of the ventilation duration and primary mode failure

**Duration of ventilation in strata of 27-30 weeks of gestational age**

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>PLV (n=26)</th>
<th>VTV (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration of ventilation h median (IQR)</td>
<td>8 (5-12)</td>
<td>5 (5-15)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**Duration of ventilation in strata of 31-34 weeks of gestational age**

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>PLV (n=32)</th>
<th>VTV (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration of ventilation h median (IQR)</td>
<td>10 (5-14)</td>
<td>5 (2-12)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

**Primary mode failure**

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>PLV (n=58)</th>
<th>VTV (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure n (%)</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
the neonatal morbidities in the two test groups the. The incidence of the ROP, IVH, PVL, necrotizing enterocolitis (NEC), and pneumothorax was similar in both groups.

Furthermore, we interestingly observed that in terms of primary mode failure (Table 2), five infants (12%) of the PCV group required HFV. In addition, out of the seven subjects who failed VG (17%), three were cross overed to the PCV mode of ventilation according to the physicians order and four required HFV. The cause for cross over to PCV was an excessive leak in the VG mode of ventilation and the reason for switch to HFV in both modes was severe hypoxemia. In both treatment groups the occurrence of primary mode failure was found to be higher in the lower gestational age group (27-30 weeks).

**Discussion**

In our study, we observed a significant reduction in the total duration of the ventilation in the VG group in infants of higher gestational age of 31-34 weeks. The possible reason for this difference may be the automatic decrease in the PIP in the VG mode as a response to improved lung compliance and thereby providing faster self-weaning from MV (5). Although there was a reduction in the total ventilation duration in the higher gestational age group, the ventilation duration did not alter significantly in the lower gestational age group of 27-30 weeks.

In a randomized study, Chowdhury et al. (6) compared the VG and PCV in terms of the time for reaching the weaning criteria in 40 preterm infants with RDS. They demonstrated that using VG did not lead to any significant difference regarding the time for reaching the weaning criteria. However, the VG was accompanied by a significant decline in the episodes of hypocarbia. Compared to the latter study, the mean gestational age and birth weight were higher in our study (26 vs. 30 w and 856 vs. 1230 g). Their findings were similar to our results in the lower gestational age group.

Regarding the duration of MV, Herrera et al. (7) noted a significant diminishing the peak and mean inspiratory pressure required during SIMV+VG ventilation, compared to the traditional pressure-controlled ventilation. These authors concluded that the low levels of mechanical support in SIMV+VG reduce the risk of ventilator-induced lung injury and the associated morbidity.

Sinha et al. in another study compared the volume-controlled ventilation (VCV) with PCV (8). They reported significantly shorter total duration of mechanical ventilation in the VCV group. Moreover, the authors observed lower incidence of BPD in the VCV group, which was not statistically significant.

Singh et al. (9) studied 90 infants ventilated mechanically with the PCV or VCV and found a trend of early weaning. In addition, they revealed shorter mechanical ventilation, decreased incidence of chronic lung disease, and less need for inhaled medications in the VCV group. In the latter study, it was stated that these findings were more consistent in the low birth weight infants (i.e., <1000 g) which is contradictory to our findings. A recent meta-analysis performed by McCallion et al. enrolling 12 randomized trials demonstrated significant reductions in short-term and long-term outcomes, such as days of ventilation and combined outcome of death or BPD (10).

Development of the ROP, IVH, PVL, and BPD is multifactorial and exposure to high levels of oxygen and low carbon dioxide for a prolonged period will lead to damage of vital organs, such as brain, retina and lungs, especially in preterm infants. According to the recent studies, it is recommended to target an oxygen saturation of 90-95% to prevent development of the ROP and BPD (11, 12). A recent study proved the relationship between the ventilator dependence and risk of ROP stating that the duration of the mechanical ventilation was found to predict ROP development with an odds ratio of 1.06 (13). However, the evidence of the ventilator mode and incidence of ROP is still lacking.

The MV might also be associated with risk of IVH. Hammad et al. studying the incidence of IVH in the mechanically ventilated patients reported that severe IVH is associated with applying MV in the delivery room, in addition to duration of the mechanical ventilation during the first three days of life (14). Furthermore, the meta-analysis

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**Table 3. Comparison of PLV with VG in terms of the neonatal morbidity**

<table>
<thead>
<tr>
<th>Neonatal morbidity</th>
<th>PLV (n=58)</th>
<th>VTV (n=57)</th>
<th>RR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy of prematurity stage 2 and above, n (%)</td>
<td>2 (5%)</td>
<td>5 (12%)</td>
<td>0.673 (0.194–0.702)</td>
<td>0.39</td>
</tr>
<tr>
<td>Intraventricular haemorrhage grade 3 and 4, n (%)</td>
<td>3 (7%)</td>
<td>2 (5%)</td>
<td>1.286 (0.319–4.08)</td>
<td>0.72</td>
</tr>
<tr>
<td>Necrotizing enterocolitis grade 2 and above, n (%)</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>0.974 (0.13–3.37)</td>
<td>0.97</td>
</tr>
<tr>
<td>Periventricular leukomalacia grade 1, n (%)</td>
<td>4 (10%)</td>
<td>3 (7%)</td>
<td>1.41 (0.29–3.44)</td>
<td>0.66</td>
</tr>
<tr>
<td>Pneumothorax n (%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>2.053 (1.635–2.577)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>5 (12%)</td>
<td>4 (10%)</td>
<td>1.25 (0.31–5.03)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
completed by Mccallion et al. reported a significant decrease in the combined outcome of PVL or grade 3-4 IVH in the VG group. Concerning the occurrence of air leak syndromes, there are controversial data about the effect of VG ventilation on air leaks (10).

In the current study, we did not find any significant difference between the groups regarding the occurrence of the outcomes, such as ROP, IVH grade 3, PVL and pneumothorax. Moreover, we observed a trend of VG mode failure in the preterm infants with gestational age of 27-30 weeks (i.e., ≤1000g), which was not significantly different between the groups. A major cause of failure was the greater difference in the delivered tidal volume and measured volume. In a study by Neumann et al. it was observed that the applied anatomical dead space associated with the equipment has a major role in tidal volume delivery in lower gestational age group of 23-32 weeks (15).

**Conclusion**

In preterm infants with RDS requiring mechanical ventilation, the VG ventilation is considered as the standard of therapy. Although in our study there was no significant difference in neonatal morbidity and mortality, there was a significant decrease in duration of the ventilation in the VG ventilation, compared to the PC ventilation in higher gestational age.

**Acknowledgments**

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**Conflicts of interests**

The authors declare no conflicts of interest relevant to this article.

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