Effect of Volume Guarantee Versus Pressure Limited Ventilation on the outcome of Preterm neonates: A randomized clinical trial.

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Abstract

Introduction: Volutrauma resulting from large tidal volumes is one of the ventilator induced lung injury which contributes to chronic lung disease. Moreover, large tidal volumes lead to hypocapnea which results in reduced cerebral blood flow, periventricular leukomalacia and poor neurodevelopmental outcomes**.** Volume guarantee (VG) ventilation is a time-cycled, pressure-limited ventilation mode which targets a set expiratory volume of gas to be delivered to the patient with each inflation. **Aim:** To compare the effect of VG Versus Pressure Limited Ventilation on the outcome of preterm neonates with respiratory distress syndrome (RDS). **Methods:** This was a randomized clinical trial conducted on 96 preterm neonates whose gestational ages ranged from 30 weeks to 34 weeks who were diagnosed with RDS and received surfactant, they were randomly allocated to two groups. The first group received VG ventilation and the second group received pressure limited (PL) ventilation. **Results:** There were no statistically significant differences in neither the duration of mechanical ventilation nor the duration of oxygen requirement between the two studied groups, however there was a statistically significant shorter duration of post extubation CPAP in the VG group (P value 0.003). Neonates ≤ 32 weeks in the VG group had a shorter duration of CPAP and oxygen requirement than those ≤ 32 weeks in the PL subgroup with P value 0.003 and 0.043 respectively. They also had less incidence of hypocapnea (P value 0.002), and a trend to less IVH and hypercapnea in comparison to the other subgroup. Neonate >32 weeks in the VG had shorter duration of CPAP than those in the PL group with a P value of 0.002 whereas there was no significant difference in other complications or mortality. **Conclusion:** Post extubation CPAP period was significantly shorter in VG group. Shorter duration of CPAP and the whole duration on oxygen therapy in smaller premature neonates <32 weeks on VG mode.

Key words: Mechanical Ventilation, Volume Guarantee, Respiratory Distress Syndrome.

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BACKGROUND

Premature infants are most vulnerable to ventilator induced lung injury (VILI), large tidal volumes can expose the infant to significant hazards; to volume trauma which exacerbates ventilator induced lung injury, contributing to chronic lung disease and to hypocapnea which can result in reduced cerebral blood flow. This is consequently associated with intra-ventricular haemorrhage, periventricular leukomalacia, and poor neurodevelopmental outcome. Volume guarantee (VG) ventilation is a time-cycled, pressure-limited ventilation mode which targets a set expiratory volume of gas to be delivered to the patient with each inflation; peak inspiratory pressure (PIP) is altered by the ventilator to achieve the set tidal volume. Control of tidal volume and minute volume may help avoid hyper- and hypocapnoea and their consequences, such as volutrauma, lung injury and alterations in cerebral blood flow **(1).**

AIM OF THE WORK

The aim of the study is to compare the effect of volume guarantee ventilation versus pressure limited ventilation on the outcome in preterm neonates with respiratory distress syndrome.

MATERIALS AND METHODS

During the study period, a total of 96 preterm neonates were included. RDS was diagnosed according to clinical findings (tachypnea, retractions, nasal flaring, cyanosis) or radiological findings (reticular granular pattern or air bronchograms) appearing within the first 24 h of life and evidence of respiratory insufficiency. Preterm neonates were intubated and ventilated according to the fixed protocols of the NICU (apnea requiring bag and mask ventilation, a need for more than 40% fractional inspired oxygen (FiO2) while on nasal CPAP at 6 cmH2O, and abnormal arterial blood gas **(2)**. After intubation, infants were randomized into 2 groups using closed envelope technique. Group 1 included infants ventilated on VG ventilation and group 2 included infants ventilated on conventional pressure limited ventilation. As blinding was difficult to achieve, the closed envelope technique, where numbered envelopes, each containing a treatment allocation were opened sequentially to avoid bias. All infants were ventilated using Drager Babylog 8000 ventilators. In group 1, the ventilation mode was SIMV, PTV, or an interchange between these two modes based on the patients' ventilation needs, along with VG mode. The targeted volume in VG was 4–6 mL/kg. Group 2 received SIMV or PTV modes without VG. Other therapeutic procedures in the two groups were principally similar.

For the VG group, the flow sensor was calibrated prior to the start of ventilation. During ventilation, the ventilator adjusted its pressures automatically to achieve the target expired tidal volume (VTe) set by the clinician. Ventilator settings were adjusted to deliver a VT of 4 -6 ml/kg. Maximum peak inspiratory pressure (PIP) was adjusted at 3-5 above PIP that achieve the set tidal volume levels to avoid pressure associated complications. FiO2 was adjusted to achieve arterial oxygen saturation (SpO2) between 92 and 95% by pulse oximeter **(2).** For infants in PL group, PIP was set manually to achieve 4–6 ml/ kg VT expired and adjusted to maintain target blood gas values at pH:7.25–7.35, PaCO2:45–55 mm Hg, PaO2:50–70 mmHg, and SpO2:92–95%. Adequacy of ventilation was assessed by periodical measurements of blood gases. The rest of the ventilator settings were similar to VG group. All infants received porcrine survanta (Curosurf) (2.5mg/kg).

Initial ventilation settings (mode of ventilation, FiO2, MAP, PIP, PEEP, rate, I:E ratio) were recorded along with the rest of admission information such as:

Full history taking including mode of delivery, history of maternal disease, gestational diabetes, hypertension, fever, rash, drug intake, radiation, premature rupture of membrane and APGAR score**, c**linical examination; birth weight, gestational age, and vital signs. Laboratory investigations: CBC, CRP, Electrolytes ABG and Cultures.

STATISTICS

Sample size

Sample size calculation was done using the comparison of duration of mechanical ventilation (MV) between preterm neonates treated with volume guarantee ventilation and those treated with pressure limited ventilation **(3).** As reported in previous publication the mean ± SD of duration of MV in volume guarantee group was approximately 3.02 ± 6.8 days, while in pressure limited group it was approximately 6.93 ± 7.8 days. Accordingly, we calculated that the minimum proper sample size was 48 neonates in each group to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level using Student's *t* test for independent samples. Sample size calculation was done using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows (*William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA*).

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Odds ratio (OR) and its 95% confidence interval (95%CI) was calculated for the complications between the 2 groups. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing normally distributed data and or large enough samples, and Mann Whitney test for independent samples in comparing not-normal data. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided *p* values less than 0.05 was considered statistically significant. IBM SPSS (*Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA*) release 22 for Microsoft Windows was used for all statistical analyse.

RESULTS

This was a randomized clinical trial which included 96 inborn preterm neonates, who were admitted to the neonatal intensive care units (NICUs), Cairo University. The median gestational age of neonates included was 32 weeks ranging from 30 to 34 weeks. The median admission weight was 2.9 Kilograms (kg) ranging from 1.1 to 3 kg. Among the 96 neonates studied, 46 were males (47.9 %) and 50 were females (52.1%) The two studied groups were statistically matched,

there were no significant differences between two groups in terms of demographic features.

Regarding the ventilation parameters, the MAP (Mean Airway Pressure) had a mean of 8.67 cmH2O and a median of 9 (5-16), the mean tidal volume was 4.8 ml and median was 5 (4-6), while mean values of PIP and PEEP were 17.2 cmH2O (12-26) and 5.4 cmH2O (4-7) respectively. However, PEEP was significantly higher in the PL group with a p-value of 0.04. Mean FiO2 was 46.3 % (21% to 100%), inspiratory time had a mean of 0.34 seconds (0.3-0.4), rate ranged between 30 to 60 with a mean of 47.4, while mean CO2 was 38.2 (25-54).

The mean number of surfactant administration was 1.1 with minimum of 1 and maximum of 3 times.

There was no significant difference neither in the duration of mechanical ventilation (MV), duration of re-ventilation, nor the duration of oxygen requirement between the two studied groups, however post extubation CPAP duration was significantly shorter in the VG group with a P value of 0.003 (**Table 1)**

There were no significant differences between the two groups in terms of complications of mechanical ventilation (MV) except for hypocapnea, which was markedly lower in the VG group than that of the PL group (P value 0.014). Other complications like pneumothorax, IVH, BPD, NEC, PVL, Sepsis, and hypercapnea showed up more in PL group but was not statistically significant. Pneumonia was more common in the VG group yet was statistically non –significant p value 0.059. There was also no statistical difference in the mortality rate between the two groups (P value 0.8) (**Table 2).**

Odds ratio was done to compare the occurrence of complications in the two groups, the only significant Odds ratio was that of hypocapnea. Patients in PL had an odds ratio of 1.6 to develop hypocapnea.

In Preterm neonates equal to or less than 32 weeks, the duration of CPAP and the duration of Oxygen requirement was significantly higher in the PL group than in the VG group with P value of 0.003 and 0.043 respectively, whereas we found no significant difference in MV duration between the two groups (**Table 3).**

In Preterm neonates ≤ 32 weeks, hypocapnea was statistically significant in the PL Group compared to the VG group with a P value of 0.002. There was also a trend to less IVH and hypercapnea in the VG group in comparison to the PL group but with a non-significant P value of 0.066 and 0.076 respectively. No statistically significant differences were detected between 2 subgroups with respect to BPD, ROP, NEC, PVL, pneumothorax and mortality with P value (1, 0.6, 0.336 ,0.306 and 0.8) respectively**.**

In Preterm neonates more than 32 weeks the duration of CPAP was significantly higher in the PL group than in the VG group with a P value of 0.003, whereas no significant differences in the MV duration nor in the duration of oxygen requirement was evident between the two groups **Table (4)** there were no significant differences in complications between the two groups.

Table (1): Comparison of VG versus PL groups in terms of oxygen treatment

	VG group				PL group					P value
	Mean+-SD	**Median**	**Min**	**Max**	**Mean**	**SD**	**Median**	**Min**	**Max**	
MV duration in (days)	5.3 +-5.86	3.7	0.33-26		4.34 +- 6		2	0.25-25		0.458
Reventiltion duration	2.98 +- 0.41	2.95	3-4		12.25 +-12.5		6.5	5-31		0.195
Total MV duration	6.04 +- 55.81	4.67	00.33-26		6.5 +-7.5		3.5	0.33-32		0.74
CPAP duration	4.19 +- 3.24	3	1-17		7.72 +-6.47		5.5	1-35		**0.003**
Duration of oxygen requirement	11.78 +- 9.38	9.5	3-47		13.96 +-9.67		10	2-50		0.318

***P value ≤0.05** is significant, **MV;** Mechanical Ventilation, **CPAP**: Continuous positive Airway Pressure*

Table (2): Showing complications of MV in the two groups

		VG		***PL***		***Total***		***P value***
		Count n=48	***%***	***Count n=48***	***% within group***	***Count***	***%***	
Pnemothorax	***Right***	*5*	*10.4%*	*6*	*12.5%*	*11*	*11.5%*	*0.379*
	Left	*0*	*0%*	*2*	*4.2%*	*2*	*2.1%*	
	Bilateral	*2*	*4.2%*	*4*	*8.3%*	*6*	*6.3%*	
	Total	*7*	*14.6%*	*12*	*25%*	*19*	*19.8%*	*0.2*
BPD		*8*	*16.7%*	*8*	*16.7%*	*16*	*16.7%*	*1.00*
IVH	***Grade 1***	*10*	*71.4%*	*7*	*43.8%*	*17*	*56.7%*	*0.2*
	Grade 2	*3*	*21.4%*	*4*	*25%*	*7*	*23.3%*	
	Grade 3	*1*	*7.1%*	*5*	*31.3%*	*6*	*20%*	
	Total	*14*	*29.2%*	*16*	*33.3%*	*30*	*31.3%*	*0.660*
NEC		*4*	*8.3%*	*7*	*14.6%*	*11*	*11.5%*	*0.336*
PVL		*1*	*2.1%*	*3*	*6.3%*	*4*	*4.2%*	*0.307*
Pneumonia		*23*	*47.9%*	*14*	*29.2%*	*37*	*38.5%*	*0.059*
ROP		*2*	*4.2%*	*3*	*6.3%*	*5*	*5.2%*	*0.6*
Sepsis		*24*	*50%*	*26*	*54.2%*	*50*	*52.1%*	*0.2*
Significant Hypercapnea		*18*	*37.5%*	*24*	*50%*	*42*	*43.8%*	*0.217*
Significant hypocapnea		*18*	*37.5%*	*30*	*62.5%*	*48*	*50%*	***0.014***
Mortality		*11*	*22.9%*	*12*	*25%*	*23*	*24%*	*0.8*

BPD; *Bronchopulmonary dysplasia on the basis of the need of an oxygen duration of ≥28 days during hospitalization* **(4)**
Pneumonia was diagnosed based on a combination of clinical, radiographic, and laboratory findings. ***IVH:*** *Intraventricular Hemorhage, NEC: Necortizing enterocolitis* ***ie:*** *Neonates with proven or advanced NEC, categorized as Bell's stage II and III, ROP: Retinopathy of Prematurity, PVL: Periventricular leukomalacia Significant Hypocapnea (PaCO2 <25 mmHg); Significant hypercapnea (PaCO2 >65 mmHg).* ***Pvalue <0.05*** *significant.*

Table (3): Comparison between duration of Oxygen requirement in patients with gestational age less than or equal to 32 weeks in the two groups.

	VG group ≤ 32 weeks (n=27)				**PL group ≤ 32 weeks (n=28)**				**P value**
	Mean	**SD**	**Median**	**Min-Max**	**Mean**	**SD**	**Median**	**Min-Max**	
MV duration in (days)	**6.14(6.93)**		**3.2**	**1-26**	**6.59(7.7)**		**2.85**	**0.25-25**	**0.691**
Total MV duration	**6.38(6.79)**		**4.33**	**1-26**	**8.16(9)**		**4.5**	**2-32**	**0.906**
CPAP duration	**4.61(4.1)**		**3**	**1-17**	**8.61(5.46)**		**7.5**	**4-25**	**0.003**
Duration of oxygen requirement	**12(12.26)**		**7**	**4-47**	**16.26(12.1)**		**13**	**2-50**	**0.043**

P value ≤0.05 *is significant,* ***MV;*** *Mechanical Ventilation,* ***CPAP:*** *Continuous positive Airway Pressure*

Table (4) Comparison between duration of Oxygen requirement preterm with gestational age more than 32 weeks in the two groups

	VG group >32 weeks No (21)				PL group >32weeks No (20)					P value
	Mean	SD	Median	Min-Max	Mean	SD	Median	Min	Max	
MV duration in (days)	5.34(3.98)		5	0.33-12	3.92 (3.99)		3	0.25-18		0.223
Total MV duration	5.6(4.360)		5	0.33-13	4.17(3.98)		3	0.34-18		0.289
CPAP duration	3.81(2.25)		3	1-10	6.83(7.39)		5	1-35		0.003
Duration of oxygen requirement	11.57(6)		12	3-20	11.53(5.4)		10	4-25		1

P value ≤0.05 *is significant,* ***MV;*** *Mechanical Ventilation,* ***CPAP:*** *Continuous positive Airway Pressure*

DISCUSSION

Volume guarantee (VG) is a modern mode of ventilation for neonates. It is a time-cycled and pressure-limited mode. In this method, peak inspiratory pressure changes according to the measured expired tidal volume in each breath. Maintaining the expired tidal volume to the level set by the operator is the end result of the process (**5).**

The initial ventilator settings; mean PIP, MAP, FiO2, RR and I:E ratio of both groups did not differ significantly. However, PEEP was significantly higher in the PL group with a p-value of 0.04 denoting a higher need for lung recruitment. The degree of lung recruitment is influenced by the level of PEEP applied to the immature lung **(6**). In our study, a higher PEEP level was needed in the PL group. This comes in contrast to the study by **Erdemir** 2013 who concluded that the mean PIP, MAP, *V*T, and RRs, PEEP of both groups did not differ significantly.

In this study we set tidal volume to 4.83±0.64 (mL/kg). The number of ABGs showing severe hypocapnoea (PaCO2 <25 mmHg) in the VG group was significantly lower than the PL group with a p value of 0.01. In addition, the number of ABGs showing severe hypercapnoea (PaCO2 >65 mmHg) was higher in the PL group than the VG but was statistically not significant. Similarly, in **Cheema 2001** study of the impact of volume guarantee ventilation on arterial Carbon Dioxide tension in preterm neonates showed that the incidence of hypocapnea was reduced from 57% in the PL group to 32% in the VG group, but this did not achieve statistical significance.

Hypocapnea is a risk factor for potential damage to the central nervous system, such as periventricular leucomalacia, intraventricular hemorrhage, cerebral palsy, cognition developmental disorder, and auditory deficiency **(7).** VG may lead to a more stable tidal volume in response to changing compliance, resistance and changing endotracheal tube leak. This produces a more stable PaCO2, with reduced frequency of hypercapnea or hypocapnea **(8).**

The difference in the duration of MV between the two groups in our study was insignificant and the number of extubation failures was equal in both groups (P value 1). Similarly, **Duman 2012** did not find a significant difference between the groups in the duration of MV in Synchronized Intermittent Positive Pressure Ventilation (SIPPV) group Vs SIPPV+VG group, p value (0.169), (**9)**. Also, **Kalane 2020** in his study Comparing Volume Guarantee Ventilation and Pressure Limited Ventilation on Required Duration of Ventilation in Preterm LBW Infants showed no significant difference between SIPPV group and SIPPV + VG group for required duration of ventilation **(10).**

Regarding the duration of CPAP similar to **Kalane 2020**, our study showed significant reduction in required duration of CPAP (post extubation) in the VG group compared to PC group (4.19±3.2), (7.7±6.4) days with (P value 0.03) in contrast to **Guven et al 2012** who demonstrated that duration of CPAP was lower in the SIMV group.

The difference in the duration of MV between the two groups in our study was insignificant and the number of extubation failures was equal in both groups (P value 1). Similarly, **Duman 2012** did not find a significant difference between the groups in the duration of MV in SIPPV group Vs in SIPPV+VG group, p value (0.169). Also, **Kalane 2020** in his study Comparing Volume Guarantee Ventilation and Pressure Limited Ventilation on Required Duration of Ventilation in Preterm LBW Infants showed no significant difference between

SIPPV group and SIPPV + VG group for required duration of ventilation.

There was no significant difference in duration of oxygen requirement in our study between the two groups with mean values of (13.9±9.6) and (11.8 ±9.3) ml/Kg respectively. This contrasts with **Kalane 2020**, where his study showed a significant reduction in duration of O2 requirement in SIPPV + VG group compared to SIPPV group.

Pneumothorax, which was highlighted as the most important side effect in this study was 63.2% in the PL group and 37.8% in the VG group, however this was statistically insignificant. **Mohagheghi** in his study on the effect of Volume Guarantee Ventilation, also demonstrated that developing pneumothorax was more possible if the patient was not ventilated by controlled volume ventilation. As VG ventilation guarantees a constant tidal volume, this leads to reduction in lung injury from overdistension, i.e., less volume trauma as pneumothorax.

In this study the prevalence of BPD was equal in the two groups, in comparison to **Erdemir 2014** where BPD was lower in VG ventilation than the other group, but the difference was not statistically significant in the VG group, however this was statistically insignificant **(11).**

There were no significant differences in incidence of NEC, ROP, PVL and IVH between both groups. Similarly, **Erdemir 2014** reported no differences observed in the neonatal complications, such as ROP and IVH between the two groups **(11). (Guven 2012)** study showed the incidences of ROP, and IVH to be significantly higher in infants in SIMV group compared with the infants in SIMV+VG group yet he showed no significant differences between two groups with respect to, NEC and PVL. Similarly, **(Singh2006)** reported no difference in the prevalence of NEC, IVH, and PVL between the two groups **(12).**

CONCLUSION

Required duration of nasal CPAP in post extubation period was found to be significantly less in VG group of infants in comparison to PL group of preterm neonates. Hypocapnea—was also significantly higher in the PL group than the VG.

Volume Guarantee ventilation can be used in preterm neonates for reducing the required duration of post extubation nasal CPAP, it also decrease the incidence of MV complications as hypocapnea .There were many limitations in this study, the most obvious limitations were the small sample size and the lack of long term follow up was a limitation, so further studies are needed to be done to corroborate these results.

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