Resultados neonatales tempranos de SIMV con volumen garantizado en recién nacidos prematuros con síndrome de dificultad respiratoria.

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Resumen

Antecedentes: El volumen garantizado (VG) de la ventilación mandatoria intermitente sincronizada (SIMV) es un nuevo modo de SIMV que proporciona un ajuste automático de la presión inspiratoria máxima para asegurar un mínimo establecido de volumen corriente y hay datos limitados sobre los efectos de la ventilación VG a corto plazo en cuanto a resultados neonatales en recién nacidos prematuros con síndrome de dificultad respiratoria (SDR).

Objetivo.

El objetivo principal de este estudio fue evaluar el efecto de la ventilación VG sobre la duración de la asistencia respiratoria y oxígeno suplementario total. También tuvo como objetivo comparar los primeros resultados neonatales de ventilación VG frente SIMV convencional en los resultados a corto plazo en los bebés prematuros con SDR que recibieron surfactante.

Método.

En este estudio aleatorizado y controlado, los recién nacidos prematuros que fueron admitidos con SDR dándoseles surfactante, se dividieron en 2 grupos: grupo 1 incluyó lactantes ventilados en SIMV convencional (n = 30) y grupo 2 incluyó recién nacidos con asistencia respiratoria con ventilación VG (n = 42). Se registraron las morbilidades neonatales como fuga de aire, displasia broncopulmonar (DBP), hemorragia intraventricular (HIV), retinopatía del prematuro (ROP), enterocolitis necrotizante (NEC), duración de la ventilación mecánica y administración de oxígeno adicional.

Resultados.

No hubo diferencias significativas entre los dos grupos en términos de características demográficas. Los recién nacidos ventilados con el modo VG tenían ventilación mecánica y necesidad de oxígeno suplementario por un tiempo más corto. La incidencia de complicaciones de DBP, ROP, HIV, relacionadas con el oxígeno a corto plazo también fueron significativamente más bajos en estos recién nacidos en comparación con los ventilados con SIMV convencional. No se encontraron diferencias significativas entre los dos grupos con respecto a NEC y fuga de aire.

Conclusión.

En conclusión, VG ventilación en combinación con el tratamiento con surfactante reduce significativamente tanto la duración de la ventilación mecánica y primeros morbilidades relacionadas con oxígeno neonatal incluyendo DBP, RP y HIV en neonatos prematuros con SDR. Estos datos favorece el uso de la ventilación respiratoria VG en apoyo de los bebés prematuros.

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Early neonatal outcomes of volume guaranteed ventilation in preterm infants with respiratory distress syndrome

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***Background*: Volume guaranteed (VG) synchronized intermittent mandatory ventilation (SIMV) is a novel mode of SIMV that provides automatic adjustment of the peak inspiratory pressure for ensuring a minimum set tidal volume and there are limited data about the effects of VG ventilation on short term neonatal outcomes in preterm infants with respiratory distress syndrome (RDS). *Objective*: The main objective of this study was to evaluate the effect of VG ventilation on duration of ventilation and total supplemental oxygen. We also aimed to compare the early neonatal outcomes of VG ventilation versus conventional SIMV on short-term outcomes in preterm babies with RDS who were given surfactant. *Methods*: In this randomized controlled study, preterm infants who were admitted with RDS and given surfactant were divided into 2 groups: group 1 included infants ventilated on conventional SIMV ($n = 30$) and group 2 included infants ventilated on VG ventilation ($n = 42$). Neonatal morbidities such as air leak, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and duration of mechanical ventilation and total oxygen supplementation were all recorded. *Results*: There were no significant differences between two groups in terms of demographic features. Infants ventilated with VG mode had significantly shorter duration of ventilation and need of total supplemental oxygen. The incidences of oxygen related short term complications including BPD, ROP, and IVH were also significantly lower in these infants compared with those ventilated with conventional SIMV. No significant differences were found between two groups with respect to NEC and air leak. *Conclusion*: In conclusion, VG ventilation in combination with surfactant treatment significantly reduced both duration of mechanical ventilation and early neonatal oxygen related morbidities including BPD, ROP and IVH in preterm infants with RDS. This data favors the use of VG ventilation in respiratory support of premature infants.**

Keywords: Early outcome, preterm, volume guaranteed ventilation, respiratory distress syndrome

Introduction

Mechanical ventilation (MV) is an important tool in the care of critically sick and preterm infants as very low birth weight (VLBW) infants may require MV therapy during their hospitalization [1,2]. The main goal of ventilator support is the maintenance of adequate gas exchange with minimum lung injury and also to reduce the work of breathing [2]. Despite increasing survival of preterm neonates, significant morbidities associated with MV still occur frequently [3,4]. Pressure damage (barotrauma), high tidal volume (volutrauma), ventilator-induced lung injury (VILI) and other organ damage are common complications of MV treatment in preterm neonates [1]. In the light of these data, as ventilation strategies were identified as the possible causes of bronchopulmonary dysplasia (BPD), the primary goal of MV is to avoid and/or minimize overdistension, atelectasis and shear stresses associated with lung injury and to prevent subsequent development of BPD.

During traditional pressure-controlled synchronized intermittent mandatory ventilation (SIMV), a fixed peak inspiratory pressure (PIP) independent of the tidal volume (TV) is delivered to the patient. Improved lung compliance after surfactant administration and/or during recovery phase of RDS, can therefore lead to delivery of involuntarily large TVs [5]. Lung overexpansion by excessive volumes and/or volutrauma may also increase the risk of both VILI and BPD. In contrast, volume guaranteed (VG) ventilation ensures a consistent expiratory VT by varying PIP [6,7]. The aim of VG ventilation is to reduce volutrauma and associated lung injury that leads to BPD by delivering a consistent TV and controlling the amount of air entering the lungs with each inflation [8–10].

Although there is no consensus regarding the optimal ventilatory strategy for the support of respiratory distress in preterm infants; volutrauma was suggested to be more important than barotrauma in the pathogenesis of BPD [11]. In a recent review including limited number of studies, volume targeted ventilation modes were reported to be associated with reduced incidence of death, BPD, hypocarbia, and pneumothorax compared with pressure limited ventilation [12]. The primary objective of this randomized controlled study was to determine the effect of VG mode on duration of ventilation and need of total supplemental oxygen in preterm infants admitted with RDS. The secondary aim was to compare the early neonatal outcomes including air leak, BPD, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and necrotizing enterocolitis (NEC) in VG ventilation versus conventional SIMV. We suggest that the results of this study may provide important data to neonatologists for the optimal ventilation strategy in premature infants.

Material and methods

The study was performed in the tertiary level neonatal intensive care unit (NICU) at Umraniye Training and Research Hospital,

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Istanbul, between February 2010 and December 2011. Preterm infants (<32 weeks' gestation and/or <1500 g) who were admitted with RDS and given surfactant within the first 2 h were included to this study. Infants with major congenital abnormalities, perinatal asphyxia and meconium aspiration were excluded. The local Ethics Committee approved the study. Written informed consent was obtained from the parents.

During the study period, a total of 90 preterm infants were eligible for the study and 72 of them were included to this study. 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 [13]. AlI infants received poractant alpha (100 mg/kg), either within 30 min of birth in infants <28 weeks or as treatment after intubation in infants ≥28 weeks. Then, infants were randomized into 2 groups by using a block randomization with random block sizes. The group 1 included infants ventilated on conventional SIMV and group 2 included infants ventilated on SIMV+VG ventilation. As blinding was impossible, random selected block sizes were used to avoid the bias and the trial authors that were active in the treatment of the infants were also kept blind to the size of each block. Based on the previous studies and with a hypothesis that VG ventilation might result with a 33% less time for achieving primary outcomes, a sample size calculation found that 45 infants per group would be required with a two sided alpha of 0.05 and power of 0.8. However, although a total of 90 infants were ventilated due to RDS during the study period, after exclusion of some infants, 72 infants were enrolled to the final analysis. Figure 1 shows the flow chart of the study group.

All infants were ventilated using a Draeger Babylog 8000 plus, a timed-cycled, continuous-flow, pressure-limited, flow-triggered neonatal ventilator, with expiratory tidal volume targeting (Software version 5; Draeger Inc., Lubeck, Germany). Two study groups were closely matched for the factors affecting the severity of RDS. Ventilator settings were adjusted according to our unit protocol: inspiratory time of 0.3–0.4 sec, rate of 60/min, maximum PIP 25 cm H_2O, positive end expiratory pressure (PEEP) 4–5 cm H_2O, circuit flow 8 l/min and maximum trigger sensitivity.

The flow sensor of the ventilator was calibrated before starting VG ventilation. During VG ventilation, the ventilator adjusted the pressure automatically for achieving the targeted VTe set by the clinician. In VG group, ventilator settings were adjusted to deliver a VTe of 4 and 5 ml/kg, for infants >1000 g and <1000 g, respectively. During SIMV + VG, all ventilator settings were the same, only the PIP limit was set 10 cm H_2O above the PIP that was used during the conventional SIMV mode. However, on the initial settings, PIP of the VG group was adjusted according to normal chest excursion with minimal PIP levels to avoid pressure associated complications. FiO_2 was adjusted to achieve arterial oxygen saturation (SpO_2) between 88 and 94% by pulse oximeter. For infants in group 1, PIP was set manually to achieve 4–5 ml/kg VT expired. and adjusted to maintain target blood gas values including pH:7.25–7.35, $PaCO_2$:45–55 mm Hg, PaO_2:50–70 mm Hg, and SpO_2:88–95%. Adequacy of ventilation was assessed by periodically measurement of blood gases. At the follow-up, the set VT was adjusted according to the arterial blood gas analysis. When the ventilatory rate was 20/min, aminophylline was started and if the infants were stable with $PaCO_2$ <60 mmHg, FiO_2 <30% and PIP <15 cm H_2O for a 8-h period, they were extubated to nasal continuous positive air pressure (CPAP). Infants were then weaned from CPAP to nasal cannula oxygen or room air, if they were stable. If a clinical deterioration was observed after extubation, reintubation and ventilation according to our unit protocol was performed in terms of the following criteria; hypercapnia (pH < 7.25; $PaCO_2$ > 60 mmHg, SpO_2 < 88% on FiO_2 < 60%), recurrent apnea (>2 episodes/h) and the need for resuscitation. An arterial line was put in all infants at admission and arterial blood gas analysis was performed.

Neonatal morbidities such as air leak, BPD, ROP, NEC, IVH, PVL, duration of mechanical ventilation and supplemental, oxygen, and duration of hospital stay were all recorded. Subgroup analysis of infants in SIMV+VG group according to the Vt was also performed. Grade 1 BPD was defined as supplemental oxygen for ≥28 days and on room air at 36 weeks postmenstrual age (PMA) or at discharge (for infants <32 weeks at birth) or at 56 days or at discharge (for infants ≥32 weeks at birth). Grade 2 BPD was defined as supplemental oxygen for ≥28 days and a need for supplemental oxygen <30% at 36 weeks PMA/discharge (for <32 weeks) or at 56 days/discharge (for infants ≥32 weeks), whereas supplemental oxygen for ≥28 days and a need for ≥30% oxygen or on nasal CPAP or mechanical ventilation at 36 weeks PMA/discharge (<32 weeks) or at 56 days/discharge (≥32 weeks) was defined as grade 3 BPD [14]. This BPD classification was preferred because we aimed to evaluate the effect of ventilation modes on both the incidence and also the severity of BPD in preterm infants. All infants were examined by the same ophthalmologist and ROP was classified according to the International Classification of ROP [15]. IVH was evaluated by cranial ultrasound examinations which were performed by the same pediatric radiologist and diagnosed using the Papile classification system. The first scan was performed within 72 h after birth and subsequently at 4 weeks of life, or earlier if clinical findings present [16]. NEC was diagnosed using modified Bell's criteria [17].

NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analysis. Descriptive statistics were

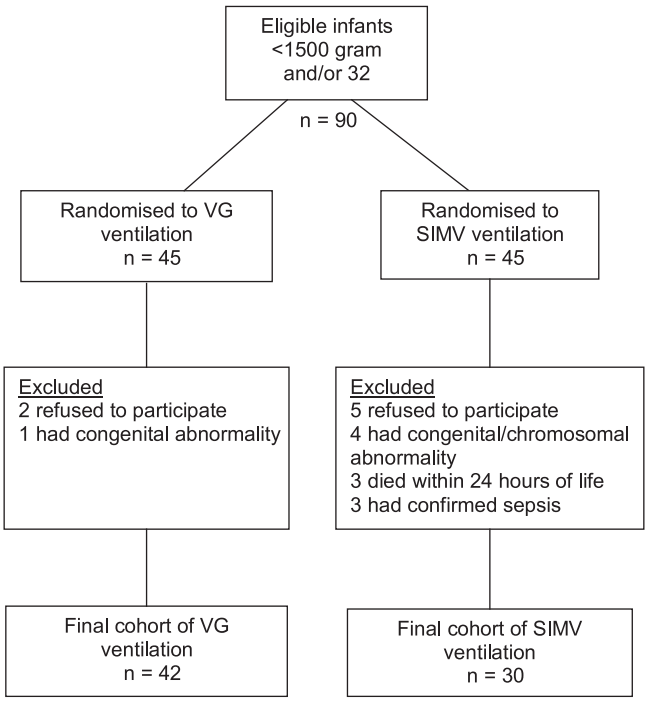

Figure 1. Flow diagram of participants in the study. VG; volume guaranteed, SIMV; synchronized intermittent mandatory ventilation.

given as mean, standard deviation and percentage. The differences between groups were evaluated with χ^2-test and Fisher's exact test for qualitative data and with Mann–Whitney *U* and *t*-tests for quantitative data. Values of $p < 0.05$ were considered significant.

Results

A total of 72 infants (40 male, 32 female) were included into the study. Mean gestational age of the infants was 29.3 ± 1.9 weeks (range 24–32 weeks) and mean birth weight was 1320 ± 349 grams (range 520–1910 g). There were 30 infants (42%) in SIMV group, and 42 infants (58%) in SIMV+VG group. Although Apgar score at minute 1 of infants in SIMV group was significantly lower than SIMV+VG group, no significant differences were detected between two groups in terms of birth weight, gestational age, gender, Apgar scores at minutes 5 and 10, need of resuscitation and antenatal corticosteroid use. Table I shows the demographic features of both groups.

The incidences of BPD, ROP, and IVH were significantly higher in infants in SIMV group compared with the infants in SIMV+VG group (all $p < 0.05$). The infants in SIMV group had an increased risk of BPD (OR, 8.57; 95% CI, 1.69–43.34), ROP (OR, 8.66; 95% CI, 2.17–34.55), and IVH (OR, 7.26; 95% CI, 2.06–25.56). There were no significant differences between SIMV and SIMV+VG groups with respect to PDA, NEC and PVL (all $p > 0.05$). No significant differences were also detected between SIMV and SIMV+VG groups in terms of neonatal sepsis, pneumonia and mortality (Table II). No air leak was detected in both groups. Although the durations of mechanical ventilation and supplemental oxygen were also significantly higher in the SIMV group compared with SIMV+VG group, in contrast, duration of CPAP was lower in the SIMV group (Table III).

Within the SIMV+VG group, the infants were subdivided into two groups: infants with a birth weight ≤1000 g and infants >1000 g. The duration of mechanical ventilation, total hospital stay and incidence of IVH were significantly higher in infants ≤1000 g in SIMV+VG group compared with those >1000 g in SIMV+VG group ($p < 0.05$). Although the incidences of BPD and ROP were significantly higher in infants with a birth weight ≤1000 g, the difference was not statistical significant ($p > 0.05$) (Table IV). Similar data were again determined in infants with a birth weight ≤1000 g that were ventilated with SIMV (Table V). When the infants with a birth weight ≤1000 g were subgrouped

Table I. Demographic features of infants in SIMV and SIMV+VG groups.

Demographic features	SIMV group ($n = 30$)	SIMV+VG group ($n = 42$)	*p* Value
Gestational age (weeks), mean ± SD	29.17 ± 1.84	29.40 ± 2.12	0.62
Birth weight (g), mean ± SD	1275.00 ± 311.63	1352.57 ± 373.83	0.36
Gender (male/female)	18/12	22/20	0.52
Apgar score at minute 1, mean ± SD (median)	5.57 ± 1.65 (6.00)	6.50 ± 2.04 (7.00)	0.02*
Apgar score at minute 5, mean ± SD (median)	7.60 ± 1.25 (8.00)	8.17 ± 1.71 (8.00)	0.07
Apgar score at minute 10, mean ± SD (median)	8.13 ± 0.97 (8.00)	8.55 ± 1.52 (9.00)	0.06
Antenatal corticosteroid, *n* (%)	22 (73)	29 (69)	0.69
Need for resuscitation, *n* (%)	8 (27)	16 (38)	0.31

*$p < 0.05$.

Table II. Frequency of neonatal morbidities in each group.

Neonatal morbidities	SIMV group $n = 30$	SIMV+VG group $n = 42$	*p* Value
Bronchopulmonary dysplasia (grade 2 and grade 3, *n* (%)	9 (30)	2 (5)	0.003**
Retinopathy of prematurity (>stage 2), *n* (%)	12 (40)	3 (7)	0.001**
Intraventricular hemorrhage (Papile grade 3 and 4), *n* (%)	13 (43)	4 (9.5)	0.001**
Necrotizing enterocolitis (>grade 1), *n* (%)	7 (23)	4 (9.5)	0.10
Patent ductus arteriosus, *n* (%)	4 (13)	4 (9.5)	0.71
Periventricular leukomalacia, *n* (%)	2 (7)	0 (0)	0.11
Neonatal Sepsis, *n* (%)	9 (30)	16 (38)	0.47
Neonatal pneumonia, *n* (%)	9 (30)	8 (19)	0.28
Mortality, *n* (%)	5 (16)	3 (7)	0.26

*$p < 0.01$.

Table III. Comparison of SIMV versus SIMV+VG groups in terms of oxygen treatment.

	SIMV group $n = 30$	SIMV+VG group $n = 42$	*p* Value
Duration of mechanical ventilation (day), mean ± SD (median)	6.93 ± 7.81 (4.00)	3.02 ± 6.76 (1.00)	0.001**
Duration of CPAP (day), mean ± SD (median)	1.20 ± 1.30 (1.00)	4.73 ± 7.44 (2.00)	0.005**
Supplemental oxygen administration (day), mean ± SD (median)	4.73 ± 7.44 (2.00)	4.45 ± 15.27 (0.00)	0.003**
Duration of hospitalization (day), mean ± SD (median)	40.00 ± 31.24 (31.50)	45.50 ± 31.43 (34.00)	0.465
Transcutaneous oxygen saturation (%), mean ± SD	93,13 ± 2,83	92,26 ± 3,53	0,672

**$p < 0.01$.

Table IV. Comparison of infants in SIMV+VG group with respect to birth weight.

Neonatal morbidities	Infants ≤1000 g, VT 5 ml/kg ($n = 10$)	Infants >1000 g, VT 4 ml/kg ($n = 32$)	*p* Value
Bronchopulmonary dysplasia (grade 2 and grade 3, *n* (%)	2 (20)	0 (0)	0.052
Retinopathy of prematurity, (>stage 2), *n* (%)	2 (20)	1 (3)	0.136
Intraventricular haemorrhage (Papile grade 3 and 4), *n* (%)	3 (30)	1 (3)	0.003**
Necrotizing enterocolitis (>grade 1), *n* (%)	2 (20)	2 (6)	0.23
Patent ductus arteriosus, *n* (%)	2 (20)	2 (6)	0.23
Duration of mechanical ventilation (day), mean ± SD (median)	7.10 ± 11.11 (2.50)	1.75 ± 4.20 (1.00)	0.031*
Duration of CPAP (day), mean ± SD (median)	3.00 ± 3.56 (2.00)	1.94 ± 1.08 (2.00)	0.738
Supplemental oxygen administration (day), mean ± SD (median)	10.40 ± 26.26 (0.00)	2.59 ± 9.64 (0.50)	0.531
Duration of hospitalization (day), mean ± SD	81.63 ± 40.35 (91.00)	36.47 ± 21.31 (30.00)	0.003**

*$p < 0.05$, **$p < 0.01$.

in terms of ventilation modes, no significant differences were detected between two groups in terms of morbidities (Table VI).

Discussion

This randomized controlled study showed that SIMV+VG ventilation significantly reduced the durations of mechanical ventilation, and total supplemental oxygen in premature infants with RDS and given surfactant. VG ventilation also significantly decreased the incidences of BPD, ROP and IVH in preterm infants and this finding might probably be associated with the use of VG ventilation. Therefore, it can be suggested that VG ventilation strategy can be used as an effective respiratory therapy in preterm infants with RDS as it had beneficial effects on decreasing both duration of ventilation and also oxygen-related morbidities.

Recent studies suggested that excessive volume, leading to overexpansion (volutrauma) might be more important in the etiology of VILI and subsequent BPD [4,5]. VG is a mode of neonatal ventilation that provides an automatic adjustment of the PIP to ensure a stable tidal volume in order to reduce lung damage and stabilize pCO_2 [6,8]. VG ventilation also allows effective control of delivered TV and ensures ventilation with significantly lower airway pressures. The automatic reduction of PIP in response to improving lung compliance provides the faster self-weaning from MV [2,6].

In a randomized study, Cheema et al. [18] evaluated 40 neonates ventilated in VG mode with assist/control (A/C) ventilation and they showed a significant reduction in PIP and MAP using VG ventilation Herrera et al. [19] reported a significant reduction in mechanical support during SIMV + VG ventilation and suggested that a lower level of mechanical support during SIMV+VG might both reduce the risk of barotrauma, volutrauma, and also associated morbidities. Sinha et al. [20] reported a significantly shorter duration of mechanical ventilation in the volume control (VC) group compared with the time-cycled pressure-limited (TCPL) group. Although the incidence of BPD in the VC group was lower, this difference was not statistically significant. In a more recent study, Singh et al. [5] found a trend toward faster weaning, reduction in the duration of ventilatory support and an improvement in the survival with VC ventilation. They also stated that these findings were more noticeable in infants with a birth weight <1000 g. Lista et al. [21] demonstrated lower levels of proinflammatory cytokines in tracheal aspirates of preterm infants ventilated with VG combined with pressure support, compared to pressure support ventilation (PSV) alone and they also reported longer mechanical ventilation duration in PSV group. In contrast, in a randomized controlled trial, preterm infants were ventilated either by pressure limited SIMV or pressure-regulated VC ventilation (PRVC) with SIMV, and no significant differences between two groups with respect to duration of mechanical ventilation were reported [22]. In a recent randomized controlled study, VG ventilation combined with A/C shortened the duration of mechanical ventilation [23]. A recent meta-analysis including twelve randomized trials also demonstrated significant reductions in days of ventilation and combined outcome of death or BPD [12]. In agreement with these studies, we determined a significant decrease in duration of mechanical ventilation and reported a lower BPD incidence in SIMV+VG group. Therefore, our findings suggest that VG might decrease the duration of mechanical ventilation and subsequent BPD development in premature infants with RDS.

BPD is the common complication related to the lung injury during the treatment of respiratory RDS. Numerous factors including birth weight, gestational age, prematurity, ventilator management, surfactant replacement, oxygen administration and pre- and post-natal inflammation are suggested to play an important role in the pathogenesis of BPD [24]. As stated above, a meta-analyses showed a significant decrease in the incidence of BPD with volume targeted ventilation compared with TCPL modes [12]. Although we performed early (<2 h of age) surfactant replacement therapy for all infants, the risk of BPD in SIMV ventilated infants was 8.5 times greater than in SIMV+VG group

Table V. Comparison of infants in SIMV group with respect to birth weight.

Neonatal morbidities	SIMV ≤1000 g (n = 7)	SIMV >1000 g, (n = 23)	p Value
Bronchopulmonary dysplasia (grade 2 and grade 3, n (%)	3 (42.8)	6 (26.0)	0.640
Retinopathy of prematurity, (>stage 2), n (%)	4 (57.1)	8 (35)	0.392
Intraventricular haemorrhage(Papile grade 3 and 4), n (%)	4 (57.1)	9 (39.1)	0.666
Necrotizing enterocolitis (>grade 1), n (%)	2 (28.5)	5 (22)	1.000
Patent ductus arteriosus, n (%)	2 (28.5)	0 (0)	0.048*
Duration of mechanical ventilation (day), mean ± SD (median)	11.86 ± 9.95 (8)	2.57 ± 1.87 (2)	0.001**
Duration of CPAP (day), mean ± SD (median)	2.43 ± 1.71 (3)	0.87 ± 0.96 (1)	0.033*
Supplemental oxygen administration (day), mean ± SD (median)	12.29 ± 12.29 (10)	2.39 ± 3.35 (2)	0.155
Duration of hospitalization (day), mean ± SD	67.57 ± 45.05 (77)	31.65 ± 24.12 (29)	0.091

*p < 0.05, **p < 0.01.

Table VI. Comparison of the neonatal morbidities in two ventilation modes in terms of birth weight.

Neonatal morbidities	Infants ≤1000 g SIMV group (n = 7)	Infants ≤1000 g SIMV+VG group (n = 10)	p Value
Bronchopulmonary dysplasia (grade 2 and grade 3, n (%)	3 (42.8)	2 (20)	0.593
Retinopathy of prematurity (>stage 2), n (%)	4 (57.1)	2 (20)	0.162
Intraventricular haemorrhage (Papile grade 3 and 4), n (%)	4 (57.1)	3 (30)	0.350
Necrotizing enterocolitis (>grade 1), n (%)	2 (28.5)	2 (20)	1.000
Patent ductus arteriosus, n (%)	2 (28.5)	2 (20)	1.000
Duration of mechanical ventilation (day), mean ± SD (median)	11.86 ± 9.96 (8)	7.10 ± 11.11 (2.50)	0.682
Duration of CPAP (day), mean ± SD (median)	2.43 ± 1.72 (3)	3.00 ± 3.56 (2.00)	0.882
Supplemental oxygen administration (day), mean ± SD (median)	12.29 ± 12.39 (10)	10.40 ± 26.26 (0)	0.139
Duration of hospitalization (day), mean ± SD	67.57 ± 45.05 (77)	81.62 ± 40.35 (91)	0.643
Neonatal Mortality, n (%)	3 (42.85)	3 (30)	0.644

*p < 0.05, **p < 0.01.

which suggested the protective role of VG ventilation against BPD development. This may be associated with stability of VT delivery by VG ventilation especially in very preterm infants who are most at risk for BPD development [25]. In a recent review, it was suggested that using volume-targeted ventilation might be a logical approach as it appeared to decrease BPD and limiting volutrauma [26]. Therefore, our results are in agreement with these data and it can be suggested that VG ventilation may be used effectively in preterm infants to decrease the incidence of BPD.

Early CPAP was found to be associated with significant decrease in duration of mechanical ventilation and also in the incidence of BPD [27]. VG ventilation provides homogeneous filling of the lung and causes less atelectotrauma, whereas lung compliance can change rapidly after surfactant treatment of RDS in VG ventilation. As lung compliance improves, the pressures generated are automatically reduced and the auto weaning occurs in VG ventilation [2]. Our protocol includes extubating preterm infants as soon as possible and to continue with nasal CPAP. In our study, duration of CPAP was significantly higher in SIMV+VG group compared with SIMV group. This can be explained with faster extubation rates after surfactant replacement in infants in SIMV+VG group.

Although the etiology of ROP, BPD and IVH is multifactorial; exposure to high oxygen levels can contribute to damage in different organs such as retina, brain and lung, especially in preterm infants. Therefore, it is suggested to minimize oxygen therapy to prevent the development of severe BPD and ROP [28]. A recent study showed that ventilator dependence was associated with increased risk of ROP and duration of mechanical ventilation was found to predict ROP development of threshold ROP with an odds ratio of 1.06 [29]. In agreement with this data, the duration of both mechanical ventilation and supplemental O_2 in SIMV group was statistically significant higher The risk of ROP development in SIMV group was also 8,6 times higher than VG group. Therefore, VG ventilation mode might prevent ROP development by decreasing the duration of oxygen therapy in these preterm infants.

MV may also increase the risk of severe IVH. In a recent study, severe IVH was both associated with the use of MV in the delivery room and duration of mechanical ventilation during the first three days of life [30]. Therefore, minimum MV support during the first days of life might decrease the risk of severe IVH in preterms. Lower incidence of IVH and abnormal periventricular echodensities were determined in infants ventilated with VG ventilation compared to those ventilated with TCPL ventilation [20]. Similarly, several other studies also reported a significant reduction in the incidence of IVH grade 3–4 or PVL in VG ventilation group [5,6,21,22,31]. Also, a recent review also found that VG ventilation resulted in a significant reduction in the combined outcome of PVL or grade 3–4 IVH [12]. In agreement with these studies, the incidence of IVH was significantly lower in VG ventilation group in our study and the risk of IVH in SIMV group was found to be 7.2 times higher than SIMV+VG group. It was suggested that control of volume and reduction of PIP might reduce severe hypo- or hypercapnea in infants ventilated with VG [6,12,20]. Therefore, it may be suggested that VG might prevent cerebral blood flow velocity fluctuations and contribute to a reduction in both IVH and/or PVL.

There are conflicting data about the effect of VTV ventilation on air leaks. Although some studies found a significant reduction in rates of pneumothorax with VTV ventilation [6, 12, 20–22], the recent review found no statistically significant difference in terms of overall incidence of any air leak [12]. We also found no differences between VG ventilation and SIMV ventilation. This difference might be associated with the design of the studies, different devices used in the studies and also the demographic features of the study populations.

Infants in SIMV+VG and SIMV groups were divided into 2 subgroups: infant ≤1000 g. Although SIMV+VG ventilation resulted in increased duration of CPAP and hospital stay in the subgroup of infants <1000 g, no statistically significant differences were detected between 2 subgroups with respect to BPD, ROP, NEC and PDA. This difference might be associated with the relatively low numbers of infants less than 1000 g in this subgroup and this might limit the power of results. The duration of mechanical ventilation was also significantly higher in infants <1000 g compared with the infants >1000 g. This is possibly associated with the immaturity of their respiratory system. Also no significant differences were detected in infants with a birth weight of <1000 g in terms of ventilation modes, therefore, this data suggest that VG ventilation may be safely used in these infants.

The major weakness of this study is the small sample size. Although it was a randomized-controlled study, infants in the conventional ventilation group remained smaller. Also, in recent years, increased use of non-invasive ventilation in this group of infants might also lead to this small study group. Another limitation of the study is that it only includes short term outcomes of the infants. Long-term follow-up of the same population will also be evaluated in a future study.

In conclusion, our study showed that VG ventilation significantly reduced the durations of mechanical ventilation, days on CPAP and total supplemental oxygen in premature infants compared with TCPL ventilation. VG ventilation also significantly decreased the incidences of BPD, ROP and IVH in preterm infants with RDS, and this data might probably be related with the use of VG strategy. In the light of these data, VG ventilation can be suggested to have beneficial effects on decreasing oxygen-related morbidities in preterm infants with RDS. Therefore, VG ventilation may be used as the first option ventilation strategy in respiratory treatment of preterm infants with RDS. However, large and more powered studies are needed to confirm these results and also to establish more precise recommendations for clinical practice.

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