Efficacy and safety of an open lung ventilation strategy with staircase recruitment followed by comparison on two different modes of ventilation, in moderate ARDS in cirrhosis: A pilot randomized trial

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Background: Mechanical ventilation in cirrhosis with acute respiratory distress syndrome (ARDS) is not widely studied. We aimed to study the effect of the staircase recruitment manoeuvre followed by two different modes of ventilation.

Methods: Thirty patients with cirrhosis with moderate ARDS underwent the staircase recruitment manoeuvre followed by randomisation to volume control or pressure control group.

Results: The PaO_2/FiO_2 ratio showed a significant improvement in both the groups after recruitment. The improvement was significantly higher in the pressure control ventilation (PCV) group at the end of the first hour as compared to the volume control ventilation (VCV) group. However, this difference was not significant at the end of 6 and 12 h. In the PCV group it improved from 118.47 ± 10.21 at baseline to 189.87 ± 55.18 12 h post-recruitment. In the VCV group it improved from 113.79 ± 13.22 at baseline to 180.93 ± 81.971. Static lung compliance also improved in both the groups significantly ($P <$ 0.001). The PCV group showed an improvement from 25.42 ± 11.94 mL/cm H_2O at baseline to 29.51 ± 14.58 mL/cm H_2O. In the VCV group the lung compliance improved from 24.78 ± 4.87 mL/cm H_2O to 31.31 ± 10.88 mL/cm H_2O.

Conclusion: This study shows that stepwise recruitment manoeuvre is an effective rescue therapy to improve oxygenation in cirrhosis with moderate ARDS. PCV may have an advantage over VCV in terms of better oxygenation.

Key Words: *cirrhosis; ARDS; recruitment; ventilation mode*

INTRODUCTION

Patients with end-stage liver disease are at risk for developing acute respiratory failure and hypoxemia secondary to hepatopulmonary syndrome, portopulmonary hypertension [1]. The presence of an exaggerated inflammatory response with a relative immunocompromised state predisposes to acute lung injury and pneumonia [2]. Respiratory abnormalities like chest wall oedema and pleural effusions (hepatic hydrothorax) decrease thoracic compliance [3]. Presence of ascites results in cephalad displacement of the diaphragm. This also reduces the respiratory muscle efficiency and increases the work of breathing [4]. This results in atelectasis and worsening pulmonary gas exchange. Acute respiratory distress syndrome (ARDS) is one of the main reasons for intensive care unit admission and mortality [2]. Mechanical ventilation is a life-supporting intervention that aims to maintain gas exchange [5]. It allows time for the lungs to heal, but it is invasive and can result in lung injury [6]. It is uncertain whether the ventilator-related injury can be reduced if the pressure delivered by the ventilator with each breath is controlled or whether the volume of air delivered by each breath is limited [7].

A Cochrane review in 2018 has suggested that the current data are insufficient to recommend a particular mode. The authors have also called for more studies to provide reliable evidence.

Shear stress contributes to ventilator-induced lung injury (VILI) [8]; hence the "open lung" concept has been advocated to keep the lung open. It consists of a recruitment manoeuvre to open the lung followed by a high positive end expiratory pressure (PEEP) application to maintain alveolar stability [8]. It has been suggested that a pressure of 45–60 cm H_2O is required to overcome the alveolar retractile force and the compressing force on the alveolus by surrounding lung tissue [9].

Metanalysis has concluded that recruitment manoeuvres result in improvement in oxygenation but may cause negative hemodynamic consequences in ARDS [10]. However, the data with regards to mechanical ventilation is nonexistent for patients with cirrhosis [11]. Therefore, the primary objective of the study was to assess the efficacy and safety of the staircase recruitment manoeuvre (SRM) in moderate ARDS in cirrhosis. The secondary objective was to study the impact of two different modes of ventilation on oxygenation post recruitment.

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RESULTS

The allocation of patients is shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1). The baseline demographic, disease severity scores, blood gas values, ventilator, and hemodynamic parameters were comparable in both the groups (Table 1). Admitted patients had high MELD (model for end-stage liver disease) and SOFA (sequential organ failure assessment) scores score in both the groups. No significant differences in terms of age, sex, oxygenation, ventilatory parameters, or hemodynamic parameters were present. The PaO_2/FiO_2 ratio was comparable at baseline in both groups ($P = 0.29$). The vasopressor support was comparable in both groups ($P = 0.54$). Presence of infection as a possible precursor to ARDS was present in 60% of patients in the PCV group and in 40% of patients in the VCV group, $P = 0.28$.

SRM showed a significant improvement in PaO_2 in the PCV and VCV group at the end of 12 h, but there was no difference between both groups ($P = 0.73$) (Table 2, Figure 2). Both groups showed a significant improvement in PaO_2/FiO_2 ratio at the end of 12 h. The improvement in PaO_2/FiO_2 ratio was significantly higher in the PCV group at the end of the first hour as compared to the VCV group (Table 2, Figure 3). The PEEP requirement was significantly higher in the volume control group at the end of 6 h and 12 h as compared to the pressure control group. Both the groups required an increase in PEEP from the baseline after the recruitment manoeuvre, which showed a trend towards significance ($P = 0.05$) (Table 2, Figure 4). The plateau pressure also reduced significantly in both

TABLE 1

Baseline demographic, clinical, blood gas, and ventilatory parameters of patients enrolled

Characteristics	PCV group (n = 15)	VCV group (n = 15)	P
Age (years)	46.87 ± 12.72	50.20 ± 14.45	0.5
BMI	26.65 ± 2.91	24.82 ± 3.77	0.14
SOFA	12.27 ± 3.150	12.40 ± 2.798	0.90
APACHE	39 ± 10.351	40.67 ± 6.673	0.60
MELD	29.33 ± 9.217	24.6 ± 9.395	0.17
CTP	12.87 ± 1.807	13.40 ± 5.316	0.71
ABG parameters and Ventilatory parameters			
pH	7.35 ± 0.05	7.33 ± 0.10	0.53
HCO_3 (mmol/L)	19.52 ± 6.85	18.96 ± 4.66	0.81
Na (mmol/L)	136.00 ± 6.72	132.73 ± 9.77	0.33
K (mmol/L)	4.600 ± 0.93	4.227 ± 0.96	0.34
Lactate (mmol/L)	6.45 ± 6.15	6.173 ± 6.35	0.90
FiO_2	50.36 ± 14.70	50.80 ± 14.45	0.93
PaO_2 (mm Hg)	79.64 ± 12.55	71.06 ± 20.45	0.18
PCO_2 (mm Hg)	39.32 ± 8.77	40.84 ± 8.86	0.64
PaO_2/FiO_2	118.47 ± 10.21	113.79 ± 13.22	0.29
PEEP (cm H_2O)	6.60 ± 0.91	7.27 ± 1.71	0.19
Tidal Volume (ml)	470.20 ± 150.09	488.21 ± 47.37	0.67
Plateau pressure (cm H_2O)	25 ± 2.50	26.64 ± 2.46	0.08
Vitals			
Heart rate (beats per minute)	90.6 ± 5.83	87.33 ± 7.57	0.19
MAP (mm Hg)	76.07 ± 22.42	83.18 ± 27.50	0.48
VIS	12.27 ± 10.81	9.79 ± 10.98	0.54
Presence of infection on day of intubation	9/15 (60%)	6/15 (40%)	0.28

Data are n (%) or mean ± S.D.

Note: APACHE = acute physiology and chronic health evaluation; BMI = body mass index; CTP = Child Turcotte Pugh score; FiO_2 = fraction of inspired oxygen; HCO_3 = bicarbonate; cm H_2O = centimeters of water; K = potassium MAP = mean blood pressure; MELD = model for end stage liver disease; mm Hg = millimeters of Mercury; Na = Sodium PaO_2 = partial pressure of arterial oxygen; PCO_2 = partial pressure of arterial carbon dioxide; Pplat = plateau pressure; PCV = pressure controlled ventilation; PEEP = positive end expiratory pressure; SD = standard deviation; SOFA = sequential organ failure score; TV = tidal volume ; VIS = vasopressor inotropic score; ABG = arterial blood gas; VCV = volume control ventilation.

the groups, ($P < 0.05$) with no difference between the groups (Table 2, Figure 5). Likewise, the static compliance also improved in both the groups, which was sustained till the end of 12 h after recruitment; however, there was no difference between both groups (Table 2, Figure 6).

One patient developed severe hypotension and bradycardia during the recruitment manoeuvre, so it was abandoned. There were no significant changes in heart rate and mean arterial pressure between the two groups or over time (Table 3). There was no significant change in the vasopressor inotrope score seen after the recruitment. (Table 3). Also, there was no difference between both groups. There was no significant difference in the length of mechanical ventilation or outcome between the two groups (Tables 4, 5).

DISCUSSION

Acute respiratory distress syndrome in cirrhosis is associated with increased mortality [14]. Deaths occurring early in the course of ARDS are mainly associated with refractory hypoxemia and late deaths are associated with progressive multiorgan failure [15]. Even without severe systemic disease, gas exchange abnormalities are common in cirrhosis due to ventilation perfusion mismatching and intrapulmonary shunting. Ascites, pleural effusions, and basal atelectasis can further worsen oxygenation [11].

Various studies on ARDS like low tidal volume ventilation, high PEEP, use of neuromuscular blockers, and recruitment strategies aim to improve oxygenation and minimize lung injury. The use of low tidal ventilation and high PEEP are standard practices in ARDS in patients with cirrhosis to improve oxygenation [2]. But the frequent presence of shock, coagulopathy, and distended abdomen preclude the use of prone positioning or extracorporeal membrane oxygenation in cases of refractory hypoxia.

To our knowledge, this the first study to evaluate the open lung ventilation strategy with staircase recruitment in patients with cirrhosis. This was similar to a study by Hodgson et al. [12] where using a decremental PEEP identified the optimal PEEP for each patient and helped in improving oxygenation and compliance. Recruitment manoeuvres are a voluntary strategy to increase transpulmonary pressure transiently to open the poorly aerated alveoli. The rationale of use in ARDS is based on the fact that the lung is derecruited (baby lung) and recruitment is possible once the minimum amount of pressure (critical opening pressure) required to maintain patency of alveoli has been reached. This results in an increase in the aerated lung mass and prevents repeated opening and closure of alveoli [16]. Other methods of recruitment like sigh and sustained inflation have been studied. Frequent occurrences of sigh episodes with high plateau pressure have raised safety concerns about the "sigh" technique [17]. Overdistension with worsening morphological and functional heterogeneity of the lung were side effects of the sustained inflation technique [18]. Hodgson et al. [12] found a reduction in the IL-8 and TNF alpha levels in patients who underwent the SRM. They required lesser episodes of rescue therapies with a lower PEEP compared with the control group.

In our study, lung compliance improved similarly but significantly in both groups over time, indicating that lung recruitment was possible and sustained throughout the study. Hodgson et al. [12] reported the improvement in lung compliance from 45 mL/cm H_2O to 49 mL/cm H_2O. The baseline compliance in our patients was approximately 25 mL/cm H_2O which improved to around 30 mL/cm H_2O. This is because patients with cirrhosis have a baseline reduced lung compliance due to the presence of ascites, atelectasis with pleural effusion, and intrathoracic chances of volume overload. Though we have not recorded these factors in individual patients, these could have been the contributing factors to the overall reduced compliance in our patients.

We found that the recruitment manoeuvre increased the lung compliance, PaO_2, and PaO_2/FiO_2 ratios significantly till 12 h after the procedure. This improvement could be attributed to the SRM as well as the increased levels of PEEP in both the groups. The improvement in the PaO_2/FiO_2 ratio was significant in the PCV group in the first hour. Though the PaO_2/FiO_2 ratios were comparable in both the groups at the

TABLE 2

Ventilatory parameters before and after recruitment

		0 h	1 h	6 h	12 h	*P*
PaO$_2$ (mean ± SD)	PCV	79.64 ± 12.55	109.07 ± 34.85	93.98 ± 24.82	97.55 ± 33.71	<0.05
	VCV	71.06 ± 20.45	93.207 ± 25.88	95.91 ± 22.29	115.29 ± 30.07	<0.05
P		0.18	0.17	0.82	0.14	
PCO$_2$ (mean ± SD)	PCV	39.32 ± 8.77	38.387 ± 7.92	38.26 ± 8.40	38.26 ± 8.89	0.63
	VCV	40.84 ± 8.86	38.05 ± 10.29	41.43 ± 7.69	40.71 ± 8.05	0.69
P		0.64	0.92	0.30	0.44	
PaO$_2$/FiO$_2$(mean ± SD)	PCV	118.47 ± 10.218	185.67 ± 52.782	179.13 ± 48.264	189.87 ± 55.187	<0.05
	VCV	113.79 ± 13.221	129.29 ± 42.253	144.64 ± 50.118	180.93 ± 81.971	<0.05
P		0.29	<0.05	0.07	0.73	
Compliance (mean ± SD)	PCV	25.42 ± 11.94	25.95 ± 11.6	28.78 ± 13.61	29.51 ± 14.58	<0.05
	VCV	24.78 ± 4.87	27.05 ± 4.06	29.83 ± 5.12	31.31 ± 10.88	<0.05
P		0.85	0.73	0.78	0.66	
PEEP (mean ± SD)	PCV	6.60 ± 0.91	8.53 ± 0.83	8.47 ± 0.91	8.53 ± 1.12	0.05
	VCV	7.27 ± 1.71	9.20 ± 1.65	9.60 ± 1.72	9.60 ± 1.72	0.05
P		0.19	0.17	<0.05	0.05	
Plateau pressure (mean ± SD)	PCV	25.00 ± 2.50	26.13 ± 2.99	25.40 ± 4.23	24.67 ± 3.67	<0.05
	VCV	26.64 ± 2.46	27.21 ± 2.19	26.00 ± 2.85	25.14 ± 2.82	<0.05
P		0.08	0.28	0.66	0.44	
Tidal Volume (mean ± SD)	PCV	470.20 ± 150.09	460.26 ± 111.32	468.66 ± 121.50	455.20 ± 124.68	0.53
	VCV	488.21 ± 47.37	482.50 ± 42.09	480.35 ± 43.16	480.00 ± 43.36	0.53
P		0.67	0.48	0.73	0.48	
pH (mean ± SD)	PCV	7.35 ± 0.05	7.37 ± 07	7.36 ± 0.08	7.35 ± 0.10	0.76
	VCV	7.33 ± 0.10	7.33 ± 0.16	7.31 ± 0.11	7.3221 ± 0.12	0.76
P		0.53	0.35	0.17	0.40	

Note: SD = standard deviation; PCV = pressure control ventilation; VCV = volume control ventilation; PEEP = positive end expiratory pressure; PaO$_2$ = partial pressure of arterial oxygen; PCO$_2$ = partial pressure of arterial carbon dioxide; FiO$_2$ = Fraction of inspired oxygen.

"0" h values are taken just before recruitment manouvre.

1 h, 6 h and 12 h values at those at the respective time after recruitment.

FIGURE 2

Trend of partial pressure of oxygen (PO2) in arterial blood gas after recruitment manouvre in pressure control ventilation and volume control ventilation groups.
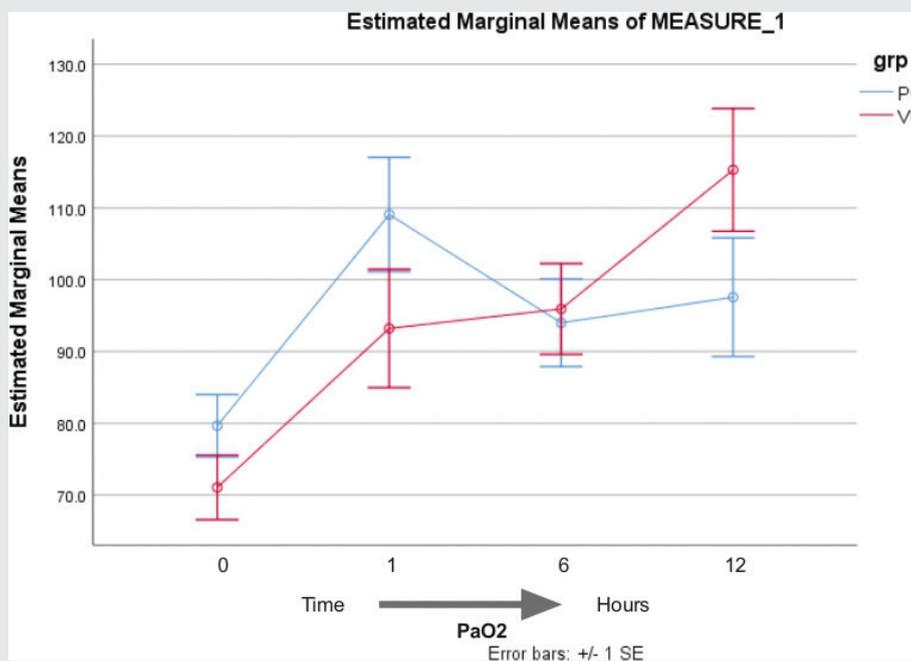
FIGURE 3

Trend in PaO$_2$/FiO$_2$ ratio after recruitment in both groups.
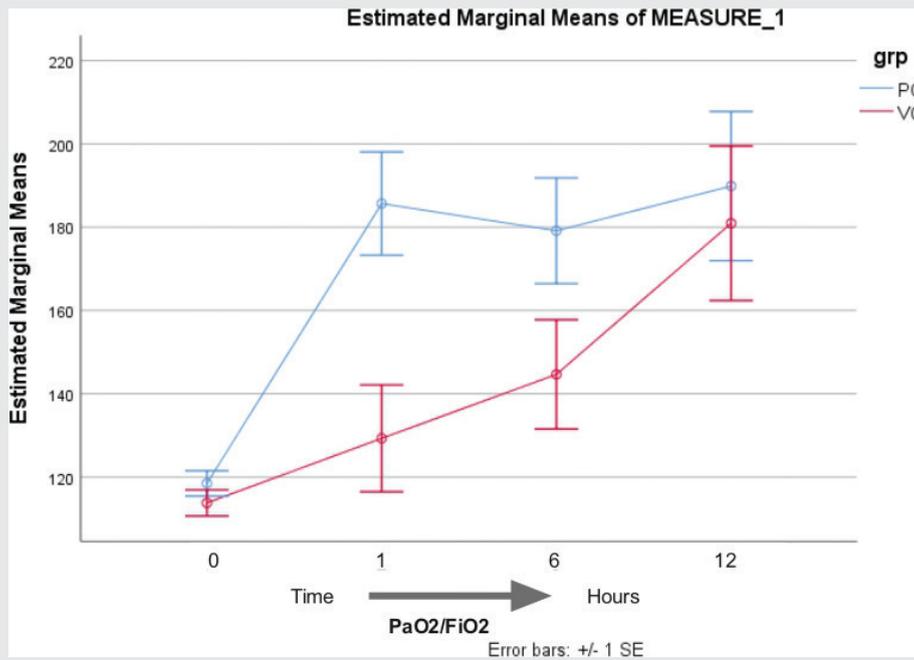
FIGURE 4

Trend of PEEP after recruitment.
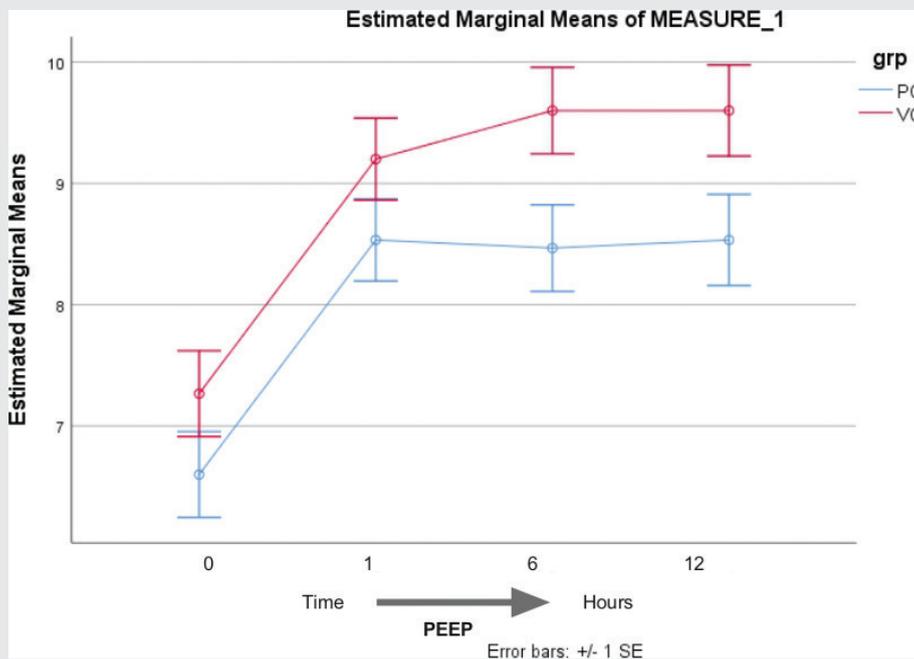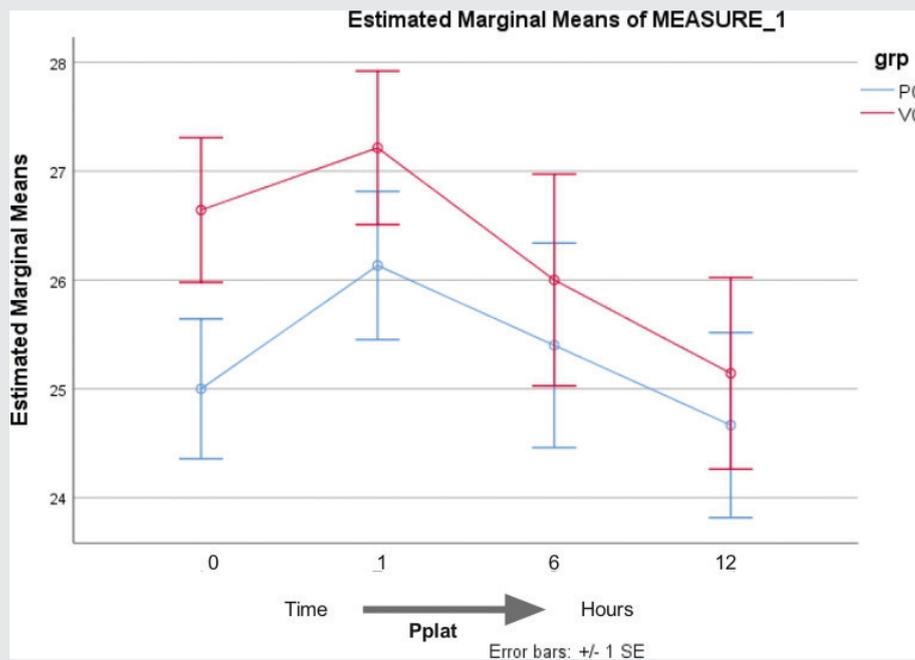
FIGURE 5

Trend of plateau pressure in both groups.

Estimated Marginal Means of MEASURE_1

FIGURE 6

Trend of static compliance in both groups after recruitment.

Estimated Marginal Means of MEASURE_1
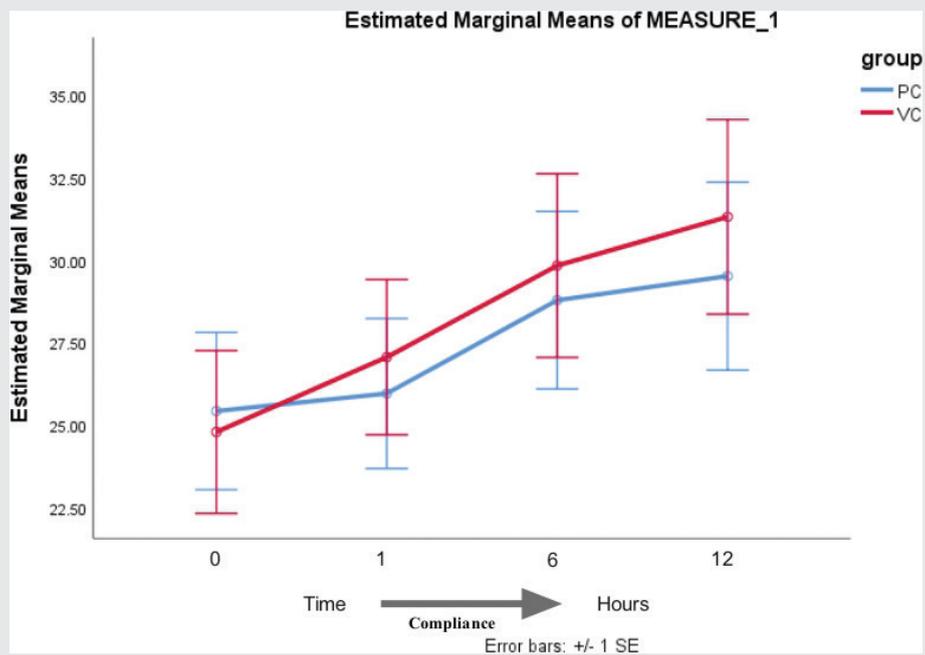
TABLE 3

Heart rate, MAP, and VIS in the patient groups before and after recruitment

		0 h	1 h	6 h	12 h	P
Heart Rate	PCV	90.60 ± 11.92	93.93 ± 20.98	91.13 ± 16.70	84.73 ± 16.329	0.70
	VCV	86.14 ± 15.34	84.64 ± 17.64	89.36 ± 18.20	89.14 ± 14.759	0.70
P		0.38	0.21	0.78	0.45	
MAP	PCV	80.67 ± 9.029	76.93 ± 8.128	81.53 ± 7.577	76.33 ± 5.665	0.07
	VCV	82.93 ± 10.709	76.57 ± 10.234	77.57 ± 14.929	78.64 ± 9.492	0.07
P		0.54	0.91	0.37	0.42	
VIS	PCV	12.27 ± 10.81	13.27 ± 12.475	10.93 ± 10.627	9.07 ± 9.513	0.18
	VCV	9.79 ± 10.98	9.57 ± 10.082	9.14 ± 8.839	8.57 ± 8.976	0.18
P		0.54	0.39	0.62	0.88	

Note: "0" h values are taken just before recruitment manoeuvre; 1 h, 6 h and 12 h values at those at the respective time after recruitment. MAP = mean arterial pressure; VIS = vasopressor inotrope score; PCV = pressure control ventilation; VCV = volume control ventilation.

TABLE 4

Length of mechanical ventilation, ICU stay

Group	PCV	VCV	P
LOMV (days)	10.33 ± 5.64	8.93 ± 4.71	0.47
Length of ICU stay (days)	12.60 ± 5.98	11.93 ± 6.37	0.77

LOMV = length of mechanical ventilation; ICU = intensive care unit; PCV = pressure control ventilation; VCV = volume control ventilation.

TABLE 5

Patient outcomes on both modes of ventilation

Outcome	PCV	VCV	P
Extubation	2/15 (13%)	1/14 (7%)	0.29
Death	10/15 (66%)	11/14 (78%)	0.23
LAMA	3/15 (20%)	2/14 (14%)	0.33

Note: LAMA = left against medical advice; PCV = pressure control ventilation; VCV = volume control ventilation.

end of 6 and 12 h, but this was at the cost of higher PEEP requirement in the VCV group as compared to the PCV group. This could be because, compared with constant flow VCV, PCV favours gas distribution between regions with heterogeneous time constants and allows a more homogeneous share of tidal volume to the whole lung through its quicker alveolar filling and more laminar flow [19]. The initial high flow rate leads to rapid alveolar inflation and improves ventilation–perfusion mismatch [20]. These advantages of PCV over VCV can be accomplished with VCV with a decelerating flow waveform [21]. However, we have used the volume control mode with a constant flow, which could explain the difference.

Similar to early proning in ARDS, early SRM may probably recruit the collapsed alveoli in the early hyaline membrane phase of ARDS before fibroblastic cell activation [22]. We performed the manoeuvre as early as 6 h after intubation, which probably resulted in the improvement in oxygenation. However, along with improvement in oxygenation, adverse events like hypotension have been reported during the procedure, which is usually transient. Hodgson et al. [12] did not report any adverse hemodynamic events during their study. They performed the SRM once daily whereas Kung et al. [22] performed it every 8 h. Kung et al. [22] reported a 50% incidence of hypotension during the manoeuvre. They also increased the PEEP by 3 cm H_2O every 3 breaths, whereas Hodgson et al. [12] increased the PEEP by 10 cm H_2O every 2 min. Therefore, the rapid escalation of PEEP and increased frequency of SRM could have contributed to the high incidence of hypotension in their study.

Patients with liver disease exhibit intense arterial vasodilatation with a reduced central blood volume, mimicking hypovolemia, and vascular hypo reactivity. The frequency of vasopressor requirement is also high in patients with liver disease and ARDS [13]; therefore, the frequency was restricted to just once. The procedure had to be abandoned in one patient

due to severe hypotension. The rest of the patients tolerated the procedure well, with no rise in vasopressor support after the procedure. The increase in pleural pressure secondary to the increase in airway pressure plays a major role in impeding venous return. However, the transmission of airway pressure to the pleural space may in part depend on the distensibility of the lungs. It has been found that in patients with lung compliance more than 45 mL/cm H_2O, 37% of the airway pressure is transmitted to the pleural space, whereas in patients with compliance less than 30 mL/cm H_2O only 24% of the airway pressure is transmitted to the pleural space [23]. This could be the reason we did not see an increase in vasopressor support despite a significant increase in PEEP after the SRM.

As evidenced by the high mortality in our study, the physiological improvements did not translate into clinically meaningful outcomes. However, it could have implications for use in patients with other critically ill patients with mild ARDS awaiting liver transplant or in immediate post-liver transplant patients who develop ARDS.

LIMITATIONS

The main drawback is the pilot study with small sample size. There was a lack of recording of other factors like effusions, degree of ascites, and the presence of hepatopulmonary syndrome that could have influenced the oxygenation and ventilator requirements in both groups.

CONCLUSION

This study shows that stepwise recruitment manoeuvre is an effective rescue therapy to improve oxygenation in cirrhosis with moderate ARDS. It should be performed as early as possible and even a single manoeuvre is effective. Pressure control ventilation may have an advantage over volume control ventilation in terms of better oxygenation with a lower PEEP requirement. However, a larger sample size could confirm this more substantially.

AUTHOR DISCLOSURES

Ethical approval

This prospective, pilot randomised controlled trial was conducted after approval by the Institutional Ethics Committee (Number: IEC/2017/51/NA07) from 1st October 2017 to 30th January 2018. All patients gave written informed consent.

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