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Conservative *versus* conventional oxygen therapy in type I acute respiratory failure patients in respiratory intensive care unit, Zagazig University

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Abstract

The present study aimed to assess the effect of a conservative (permissive hypoxemia) *versus* conventional (normoxia) protocol for oxygen supplementation on the outcome of type I respiratory failure patients admitted to respiratory intensive care unit (ICU). This randomized controlled clinical trial was carried out at the Respiratory ICU, Chest Department of Zagazig University Hospital, for 18 months, starting in July 2018. On admission, 56 enrolled patients with acute respiratory failure were randomized in a 1:1 ratio into the conventional group [oxygen therapy was supplied to maintain oxygen saturation (SpO_2) between 94% and 97%] and the conservative group (oxygen therapy was administered to maintain SpO_2 values between 88% and 92%). Different outcomes were assessed, including ICU mortality, the need for mechanical ventilation (MV) (invasive or non-invasive), and ICU length of stay. In the current study, the partial pressure of oxygen was significantly higher among the conventional group at all times after the baseline reading, and bicarbonate was significantly higher among the conventional group at the first two readings. There was no significant difference in serum lactate level in follow-up readings. The mean duration of MV and ICU length of stay was 6.17±2.05 and 9.25±2.22 days in the conventional group *versus* 6.46±2.0 and 9.53±2.16 days in the conservative group, respectively, without significant differences between both groups. About 21.4% of conventional group patients died, while 35.7% of conservative group patients died without a significant difference between both groups. We concluded that conservative oxygen therapy may be applied safely to patients with type I acute respiratory failure.

Introduction

Oxygen therapy is widely used in the clinical field as a safe and crucial therapeutic approach. In standard liberal oxygen therapy, oxygen is given to most patients above their normal level to avoid the hazards of tissue hypoxia [1].

Hypoxemia develops when the oxygen supply to the tissues becomes inadequate to satisfy oxygen needs, as measured by the low partial pressure of arterial oxygen (PaO_2). Hypoxemia is considered a detrimental insult, mainly in severely ill patients [2]. Oxygen supplementation, either non-invasively or invasively, is commonly used in hospitals to prevent and treat hypoxemia [3]. Acute respiratory failure, which is indicated for mechanical ventilation (MV), is considered one of the most common causes of intensive care unit (ICU) admission [4].

Many critically ill patients are exposed to excess oxygen therapy. Indeed, hypoxia can cause cell injury and increase mortality, so adequate oxygen supply is mandatory; however, hyperoxia, due

to oxidative stress and inflammatory processes, can induce tissue damage [5,6].

It is a difficult task to maintain adequate oxygen targets in critically ill patients. Many researchers have identified that liberal or conventional oxygen therapy strategies among adult critically ill patients can cause more mortality and adverse effects than the conservative oxygen therapy strategy [7-9]. Other recent studies, including type I respiratory failure patients or mechanically ventilated patients, detected that the clinical outcomes of either liberal or conservative oxygen therapy groups were statistically insignificant [10,11]. Despite this, the already-published oxygen therapy guidelines about the criteria for oxygen therapy and targets are different and conflicting. So, a lot of studies were conducted about the different oxygen therapy regimens and their effects on respiratory failure patients' prognosis. However, their conclusions have not been closely consistent with each other [1].

So, the present study aimed to assess the effect of a conservative (permissive hypoxemia) *versus* conventional (normoxia) protocol for oxygen supplementation on the outcome of type I respiratory failure patients admitted to the respiratory ICU.

Materials and Methods

This study was a randomized controlled clinical trial that was conducted at the Respiratory ICU (RICU), Chest Department, Zagazig University Hospital, for 18 months starting in July 2018, after approval from the Zagazig University-Institutional Review Board (ZU-IRB No. 4719/25-6-2018).

Patients

All type I acute respiratory failure patients admitted to RICU, Zagazig University Hospitals for 18 months starting in July 2018 were included.

Inclusion criteria

Inclusion criteria are i) all patients with acute type I respiratory failure due to a pulmonary cause; ii) aged 18 years and older; iii) the duration of the ICU stay is expected to be equal to or greater than 72 hours.

Exclusion criteria

Exclusion criteria are i) pregnant women; ii) patients with non-pulmonary causes of respiratory failure; iii) presence of multiple organ failure on admission; iv) hemodynamic instability (need for vasopressor or inotropic drugs) on admission.

Sample size

Using open epi, the sample size was calculated to be 56 (28 in each group), assuming that the mean ± standard deviation (SD) of ICU length of stay of patients with conventional *versus* conservative oxygen therapy was 5±1.5 *versus* 4±1.1, respectively, at 80% power of the test and 95% confidence level.

On admission, enrolled patients were randomized into the conventional group (group A) and conservative group (group B) with a ratio of 1:1. In the conventional group, each patient received a fraction of inspired oxygen (FiO_2) with target pulse oximeter oxygen saturation (SpO_2) between 94% and 97% (normoxemia). If the SpO_2 dropped below 94, the FiO_2 was elevated to obtain the target SpO_2 value. In the conservative group, each patient received the lowest possible FiO_2 to reach the target SpO_2 values between 88% and 92% (permissive hypoxemia) [12,13].

All patients in both groups received oxygen therapy *via* different oxygen masks or MV (either invasive or non-invasive) when indicated by the failure of the former oxygen masks.

Operational design

The following was done: i) informed and written consent was taken from patients or their surrogate decision-makers; ii) thorough medical history and comorbidities from patients or relatives and documents; iii) complete medical examination; iv) pre-existing investigations, *e.g.*, pulmonary function test, computed tomography (CT) chest, echocardiography; v) the simplified acute physiology score (SAPS) 3 score was calculated for all patients to assess their disease severity at the time of ICU admission [14]; vi) continuous SPo_2 monitoring; vii) arterial blood gases sampling at least once daily; viii) full laboratory investigations, *e.g.*, complete blood count, liver function tests, kidney function tests, serum lactate, serum electrolytes at admission and through the hospital course; ix) radiological investigations: chest X-ray, CT chest if needed, echocardiography if needed; x) microbiological samples according to clinical need; xi) central venous oxygen saturation ($ScvO_2$): central venous blood sample was taken in patients with central line daily to measure $ScvO_2$ after aspiration of 20 mL of blood to avoid the frequent catheter flushing effect. Reinjection of the aspirated blood was done after sampling. Interpretation of $ScvO_2$ level: high level if more than 75%, normal level if 65-75%, and low level if less than 65% [15]; xii) venous partial pressure of carbon dioxide (PCO_2) and arterial PCO_2 difference [$P(v\text{-}a)CO_2$]: the venous PCO_2 was measured from the central venous blood sample *via* a central venous catheter [15]; xiii) the co-existence of central venous-to-arterial CO_2 difference (less than 6 mmHg), $ScvO_2$ (more than 70%), and lactate (less than 2 mmol/L) indicate the adequacy of the oxygen delivery (DO_2) to the tissues [15].

Outcome definition

Outcome definition includes i) ICU mortality (30-day mortality) or discharge; ii) number of days on MV; iii) length of stay in ICU.

Administrative design

Approval from the Zagazig University-Institutional Review Board (ZU-IRB No. 4719/25-6-2018) was obtained.

Statistical analysis

Statistical Package for the Social Sciences (SPSS version 20.0, IBM, Armonk, NY, USA) software was used for analysis. According to the data type, the quantitative continues group is represented by the mean ± SD, the qualitative one is represented by the number and percentage; differences and the association of the qualitative variable are represented by the Chi-square test (X^2). The 30-day mortality of both groups was compared using Kaplan-Meier survival analysis. Differences between quantitative independent groups were obtained by *t*-test; $p<0.05$ was set for significant results and $p<0.001$ for highly significant results.

Results

The current study included two groups: the conventional group, in which 28 patients received FiO_2, allowing SpO_2 target between 94

and 97%, while the second (conservative group of 28 patients) received oxygen therapy at the lowest possible FiO_2 to maintain SpO_2 values between 88 and 92%.

Both groups were matched regarding age, SAPS 3 score, and sex. Group B patients (conservative oxygen group) were older (52.75±8.94 years) *versus* 48.89±9.76 years in group A (conventional oxygen group). Also, group B patients had a higher SAPS 3 score (31.40±8.36) than group A (28.52±7.36), but there was no statistically significant difference between the two groups regarding either mean age or SAPS 3 score. Pneumonia was the most prevalent cause of ICU admission in both groups. Pneumonia prevailed in 60.7% and 71.4% within conventional and conservative groups, respectively, while interstitial lung diseases were equally distributed within both groups (17.9%); the same was true for pulmonary embolism, which prevailed in 7.1% within each group. Bronchial asthma occurred in 14.3% and 3.6% of the conventional and conservative groups, respectively. There was no statistically significant difference between both patient groups regarding the original cause of acute respiratory failure (Table 1).

About one-third of each patient group had co-morbidities without statistically significant differences between them. About 67.9% and 60.7% within conventional and conservative groups, respectively, had no comorbidities. Hypertension was equally distributed within both groups (14.3%), as was the case for both gastroesophageal reflux disease and diabetes-hypertension, which prevailed in 3.6% of each group (Table 1).

Group A was significantly higher regarding SpO_2 and FiO_2 after the baseline until the end day. This means that to achieve the desirable conventional saturation, a higher FiO_2 was needed in contradiction with conservative saturation (Figure 1 A,C). Also, group A was significantly higher regarding arterial oxygen saturation (SaO_2) after the baseline until the end day, with a mean SaO_2 on the first day being 94.05±3.74% and 87.66±2.01% in conventional and conservative groups, respectively (Figure 1B).

Group A received a lower positive end-expiratory pressure (PEEP), which was statistically significant during the first and second days only. Group B patients were more frequently subjected to higher PEEP settings, as the highest PEEP (mean±SD) applied to group A and group B were 7.85±1.95 and 9.80±2.04 cm H_2O, respectively. There is no significant difference between both patient groups regarding PaO_2/FiO_2, $ScvO_2$, and the central venous to arterial PCO_2 difference (Table 2).

It was found that pH was significantly higher among group A on the first day of oxygen therapy, and on the last day, PaO_2 was significantly higher among group A at all times after base. There was no significant difference between patient groups regarding PCO_2. Bicarbonate was significantly higher in group A at the first two readings after the base (Table 3). In group A, serum lactate was significantly lower on the first day only (Table 4).

It was found that invasive MV was needed in 25% of group B patients and 14.3% of group A patients to achieve the desirable saturation. There was no significant difference between groups regarding ICU stay and MV duration. About 21.4% of patients died in group A, while 35.7% died in group B without a significant difference between both groups (Table 5). One patient in each group was mechanically ventilated for more than 10 days.

The overall survival duration (mean±SD) was 23.76 ± 2.58 days: for group A 24.45±2.58 days and for group B 23.50±2.27 days. Survival analysis showed that survival was nearly the same in both groups (Figure 2).

Discussion

Critically ill patients with acute type I respiratory failure are managed by supplemental oxygen therapy; however, the benefits and hazards of various oxygenation targets are vague [11]. Many studies have concentrated on the arterial oxygenation targets or the FiO_2 in these patients; how to manage the oxygenation targets in critically ill patients is still a debated issue. A liberal oxygen therapy (lowest SpO_2 target: 96-97%) could cause higher mortality and more adverse events than the conservative oxygen therapy strategy among adult ICU patients [8].

Conservative oxygenation therapy (minimum target SpO_2: 88-94%) to avoid the deleterious effects of hyperoxemia has been applied with promising results in acute respiratory distress syndrome (ARDS) patients and other acutely ill patients [9]. However, continued efforts to achieve normoxemia in critically ill patients with persistent low arterial oxygenation may be more detrimental than accepting some degree of hypoxemia [16].

Table 1. Patients' characteristics of both studied groups.

Items			Group A (conventional)	Group B (conservative)	T/X^2	p value
Age (Y) (mean±SD			48.89±9.76	52.75±8.94	1.541	0.129
SAPS 3 (mean±SD)			28.52±7.36	31.40±8.36	1.631	0.108
Sex	Female	n (%)	11 (39.3)	9 (32.1)	1.22	0.54
	Male	n (%)	17 (60.7)	19 (67.9)		
Pre-existing disease	Bronchial asthma	n (%)	4 (14.3)	1 (3.6)	4.23	0.32
	ILD	n (%)	5 (17.9)	5 (17.9)		
	PE	n (%)	2 (7.1)	2 (7.1)		
	Pneumonia	n (%)	17 (60.7)	20 (71.4)		
	Total	n (%)	28 (100.0)	28 (100.0)		
Co-morbidities	NO	n (%)	19 (67.9)	17 (60.7)	3.54	0.59
	DM	n (%)	2 (7.1)	5 (17.9)		
	DM, HTN	n (%)	1 (3.6)	1 (3.6)		
	GERD	n (%)	1 (3.6)	1 (3.6)		
	HTN	n (%)	4 (14.3)	4 (14.3)		
	HTN, GERD	n (%)	1 (3.6)	0 (0.0)		
	Total	n (%)	28 (100.0 %)	28 (100.0)		

T, *t*-test; X^2, Chi-square test; SAPS 3, simplified acute physiology Score 3; ILD, interstitial lung diseases; PE, pulmonary embolism; DM, diabetes mellitus; HTN, hypertension; GERD, gastroesophageal reflux disease.

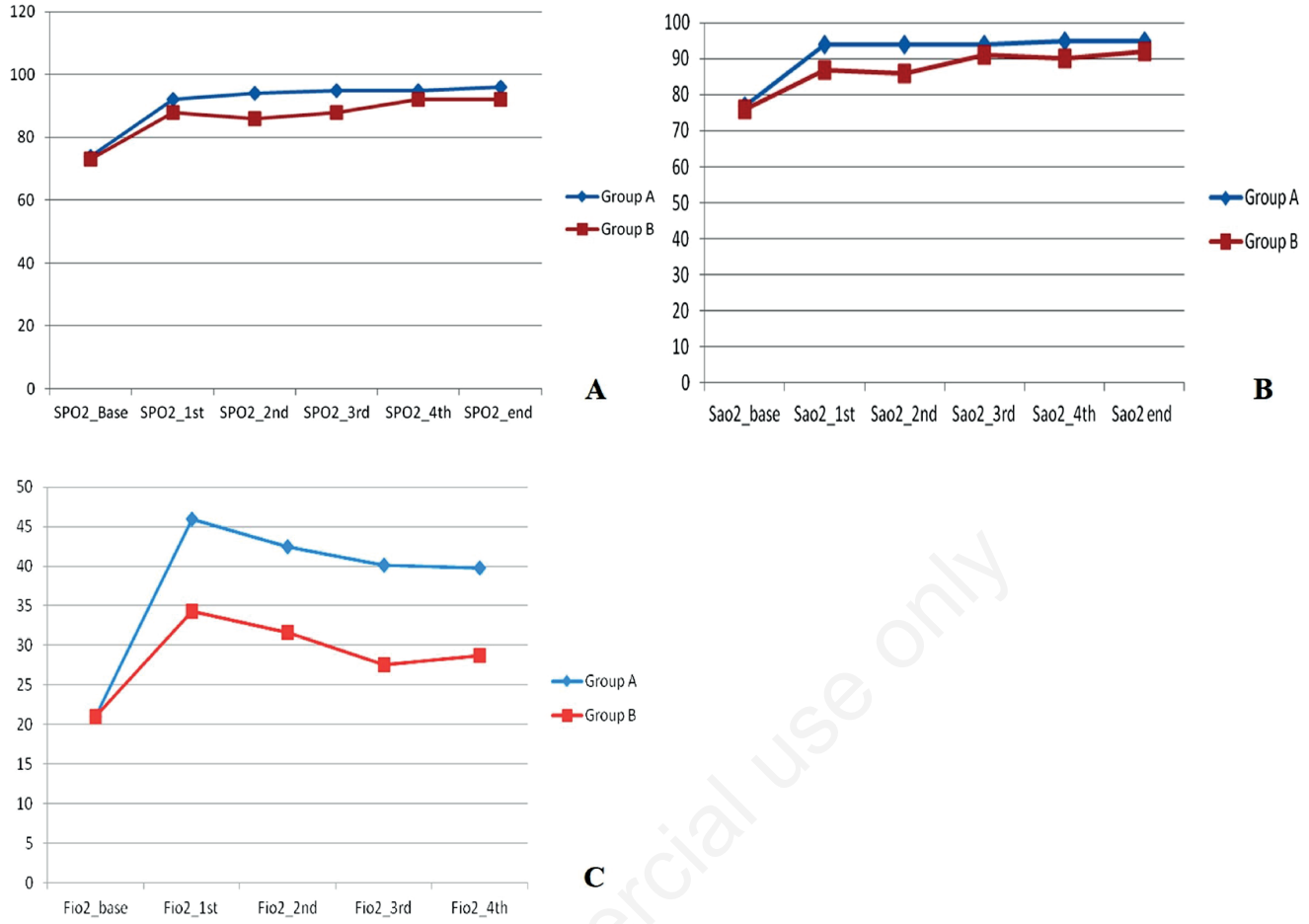

Figure 1. Line graphs illustrated mean ± standard deviation of: A) pulse oximeter oxygen saturation (SpO_2) at different times of follow-up among studied groups; B) arterial oxygen saturation (Sao_2) distribution at different times of follow-up among studied groups; C) fraction of inspired oxygen (FiO_2) needed in each group to achieve the desirable saturation at different times of follow up.

Table 2. Positive end-expiratory pressure, partial pressure of arterial oxygen/fraction of inspired oxygen and central venous oxygen saturation distribution at different times of follow-up among the studied groups.

Items	Group A (conventional)	Group B (conservative)	T	p value
PEEP 1st	7.20±1.98	9.80±2.04	3.345	0.002*
PEEP 2nd	7.25±2.0	9.23±2.11	2.169	0.041*
PEEP3rd	7.85±1.95	8.88±1.47	1.337	0.223
PEEP 4th	7.55±2.03	8.46±1.70	0.928	0.368
PEEP end	7.14±1.95	7.90±1.66	0.861	0.403
PaO_2/FiO_2_1st	120.36±28.63	129.36±32.6	1.469	0.095
PaO_2/FiO_2_2nd	122.3±29.36	128.63±32.63	1.334	0.185
PaO_2/FiO_2_3rd	155.41±53.2	161.85±49.9	0.810	0.365
PaO_2/FiO_2_ 4th	185.36±62.3	182.63±59.36	0.964	0.211
PaO_2/FiO_2_end	198.52±54.2	197.36±68.63	0.655	0.412
Central venous O_2 sat 1st (percent)	48.40±7.36	46.0±3.25	0.654	0.423
Central venous O_2 sat 2nd	58.40±10.45	56.0±2.58	0.443	0.671
Central venous O_2 sat 3rd	64.40±12.60	52.0±0.81	1.937	0.094
Central venous O_2 sat 4th	74.40±12.60	72.0±0.81	1.937	0.094
Central venous to arterial PCO_2 difference	5.64±1.03	5.46±1.16	0.449	0.657

*significant p value; T, *t*-test; PEEP, positive end-expiratory pressure; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; O_2 sat, oxygen saturation; PCO_2, partial pressure of carbon dioxide.

Table 3. Arterial blood gas distribution at different times of follow-up among the studied groups.

Items	Group A (conventional)	Group B (conservative)	T	p value
PH base	7.44±0.02	7.43±0.04	0.793	0.431
PH 1st	7.42±0.02	7.40±0.01	2.329	0.031*
PH 2nd	7.41±0.03	7.40±0.005	1.269	0.220
PH 3rd	7.43±0.03	7.41±0.019	2.047	0.056
PH 4th	7.41±0.02	7.41±0.008	1.004	0.329
PH end	7.44±0.007	7.39±0.01	5.244	0.001*
PaO_2 base (mmHg)	50.66±7.92	49.35±6.40	0.737	0.412
PaO_2 1st	62.85±9.11	53.45±4.29	3.608	0.002*
PaO_2 2nd	68.16±16.66	59.23±1.36	2.850	0.009*
PaO_2 3rd	72.71±10.54	56.81±6.52	3.978	0.001*
PaO_2 4th	75.83±4.44	59.54±2.84	9.276	0.00*
PaO_2 end	76.65±5.36	61.36±3.11	8.523	0.00*
PaO_2 base (mmHg)	35.66±12.03	32.21±4.07	1.866	0.075
PCO_2 1st	37.57±2.63	32.12±0.35	1.569	0.141
PCO_2 2nd	37.14±3.48	35.50±0.53	1.323	0.209
PCO_2 3rd	38.16±3.97	36.75±0.70	1.001	0.336
PCO_2 4th	37.0±4.14	37.87±0.83	0.589	0.567
PCO_2 end	36.25±1.95	38.10±1.34	1.938	0.052
HCO_3 base (mmol/l)	23.07±1.91	22.86±1.86	0.937	0.265
HCO_3 1st	24.08±1.50	21.88±0.43	3.957	0.002*
HCO_3 2nd	23.84±1.05	22.36±0.21	3.905	0.002*
HCO_3 3rd	23.55±1.02	22.88±0.35	1.714	0.112
HCO_3 4th	24.13±0.66	23.12±0.99	2.143	0.053
HCO_3 end	23.97±1.43	22.50±1.37	1.631	0.142

*significant p-value; T, *t*-test; PaO_2, partial arterial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; HCO_3, bicarbonate.

Table 4. Serum lactate distribution at different times of follow-up among the studied groups.

Items			Group A (conventional)	Group B (conservative)	T	p value
S lactate base (mmol/l)			1.70±0.58	2.01±1.01	1.376	0.166
S lactate 1st			1.43±0.52	1.85±0.65	2.737	0.012*
S lactate 2nd	1.52±0.40	1.66±0.76	1.373	0.172		
S lactate 3rd	1.62±0.53	1.68±0.88	0.949	0.325		
S lactate 4th	1.44±0.52	1.48±0.74	1.574	0.098		
S lactate end	1.88±0.08	1.54±0.59	1.231	0.239		

*significant p-value; T, *t*-test; S, serum.

Table 5. Patients' outcomes regarding the need for non-invasive ventilation or mechanical ventilation, duration of mechanical ventilation, intensive care unit stay, and mortality among studied groups.

			Group A (conventional)	Group B (conservative)	X^2	p value
MV	Not	n (%)	22 (78.5)	16 (57.1)	3.05	0.21
	NIV	n (%)	2 (7.2)	5 (17.8)		
	MV	n (%)	4 (14.3)	7 (25.0)		
	Total	n (%)	28 (100.0)	28 (100.0)		
Outcome	Died	n (%)	6 (21.4)	10 (35.7)	1.42	0.23
	Discharged	n (%)	22 (78.6)	18 (34.3)		
	Total	n (%)	28 (100.0)	28 (100.0)		
					T	p value
Duration MV (days)		mean ± SD	6.17±2.05	6.46±2.0	0.526	0.601
ICU stay (days)		mean ± SD	9.25±2.22	9.53±2.16	0.487	0.628

T, *t*-test; X^2, Chi-square test; MV, mechanical ventilation; NIV, non-invasive ventilation; ICU, intensive care unit; SD, standard deviation.

The objective of the current study was to assess the effect of two oxygen therapy protocols on the outcome of type I respiratory failure patients admitted to the RICU.

This study is considered one of the few research that studied the outcome of normoxemia *versus* permissive hypoxemia for type I respiratory failure patients due to different pulmonary causes, as evidenced by Gilbert-Kawai *et al*. [17], who concluded that up to now, only a few researchers have studied a comparison between "normal" or "conventional" *versus* "low" or "permissive" oxygenation strategies for respiratory failure patients.

In the current study, the conservative group of oxygen therapy with a SpO_2 target between 88% and 92% was matched with the lower oxygen therapy targets; in other studies, including Schjørring *et al*. [11], randomly recruited ICU patients with hypoxemic respiratory failure received oxygen therapy in the lower oxygenation group with a PaO_2 target (60 mmHg) *versus* a higher-oxygenation group with a PaO_2 target (90 mmHg). Barrot *et al*. [13] allocated ARDS patients to use liberal oxygen therapy (target SpO_2 equal 96% and PaO_2 between 90 and 105 mmHg) *versus* conservative oxygen therapy (target Spo_2 between 88 and 92% and PaO2 between 55 and 70 mmHg) for 7 days. Also, Panwar *et al*. [12] applied conservative oxygen therapy with a SpO_2 target of 88-92% for severe acute type I respiratory failure patients.

However, in the current study, the SpO_2 target (between 94% and 97%) in the conventional oxygen group was lower than the SpO_2 targets (mostly more than 96%) of the conventional oxygen therapy in other studies [11,13].

In the current study, group A (the conventional group) was significantly higher regarding SPO_2, SaO_2, and FiO_2 after the base until the end of the study. These findings are in line with those of Panwar *et al*. [12] and Chen *et al*. [18], who demonstrated that the mean/SpO_2, SaO_2, PaO_2, and FiO_2 were statistically higher in the liberal (conventional) group compared with the conservative group. Hirase *et al*. [9] studied 172 patients using conservative oxygen therapy (lowest SpO_2 target between 88% and 94%) and 370 patients using conventional oxygen therapy (lowest SpO_2 target between 96% and 97%). Their conservative oxygenation group showed significantly lower rates of SpO_2 in comparison with the conventional oxygenation group.

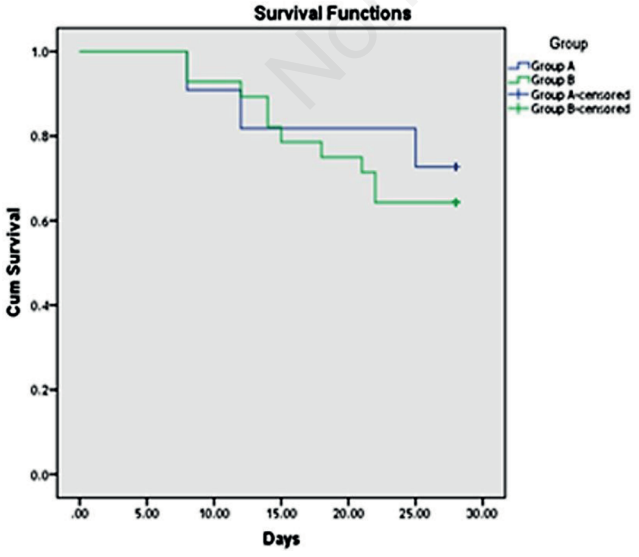

Figure 2. Line graph showing survival functions among studied groups using Kaplan-Meier.

Throughout the present study, the given FiO_2 to both patients' groups remains within the safest range without reaching the toxic level, as its maximal mean was 45.95±11.91% *versus* 34.37±23.15% in the conventional and conservative groups, respectively. Similarly, the FiO_2 applied to both conventional and conservative groups was 0.39 *versus* 0.36 in the Girardis *et al*. study [19] and 0.36 *versus* 0.26 in the Panwar *et al*. study [12]. Oxygen toxicity is seldom developed if the FiO_2 is less than 0.5. Also, positive pressure ventilation with a high FiO_2 (0.61-0.93) caused characteristic pathological insults independent of the other deleterious effects of mechanical ventilators [16].

In our study, there was no statistically significant difference between both patient groups regarding the MV duration and length of ICU stay. Also, Panwar *et al*. [12] and Girardis *et al*. [19] revealed no statistically significant difference between groups as regards the MV period. Many studies revealed that the oxygen therapy strategy could not have an effect on the ICU length of stay [20-22].

Our study revealed that group A significantly received lower PEEP as PaO_2 was also significantly higher among group A at all times, so this group needed less PEEP. On the other side, more patients with pneumonia (20 patients) were present among group B patients who needed higher PEEP.

Currently, there is no significant difference in central venous to arterial PCO_2 between both patient groups. The mean values were 5.64±1.03 mmHg for group A and 5.46±1.16 mmHg for group B. We studied the central venous-to-arterial PCO_2 difference as an indicator of adequate DO_2 to the tissues.

He *et al*. [23] defined systemic DO_2 as the product of cardiac output and arterial oxygen content, which is significantly affected by SaO_2. So, DO_2 should be assessed when permissive hypoxemia is applied. The co-existence of a central venous-to-arterial CO_2 difference (less than 6 mmHg), $ScvO_2$ (more than 70%), and lactate (less than 2 mmol/L) indicate the adequacy of DO_2. Yuan *et al*. [24] stated that P(v-a)CO_2 is an important measure during the resuscitation of sepsis as it is an important measure of the adequate venous flow that can carry the CO_2 released from the different tissues. High P(v-a)CO_2 indicates low tissue perfusion and insufficient cardiac output.

The present study showed that group A patients had a significantly lower serum lactate level The present study showed that group A patients had a significantly lower serum lactate level (p=0.012) on the first day only (1.43±0.52 *versus* 1.85±0.65 mmol/L); the highest serum lactate level measured throughout the current study was 2.01±1.01 mmol/L in group B as a baseline reading, but all subsequent serum lactate levels in both patients' groups were less than 2 mmol/L, *i.e.*, we did not record any hyperlactatemia during our study. Suzuki *et al.* demonstrated low serum lactate levels in their conservative oxygen therapy group during the first 10 days (p=0.08), so the conservative oxygen therapy (SpO_2 targets were 90-92%) was safe and accompanied by a decrease in lactate levels and less non-pulmonary organ dysfunction [25].

Panwar *et al*. [12] found that the mean serum lactate in the conservative oxygenation and liberal oxygenation groups was 1.9 mmol/L and 1.7 mmol/L, respectively, with no significant difference. Barrot *et al*. [13] found that the conservative and conventional groups had higher serum lactate levels than our study did (2.2±1.4 mmol/L *versus* 2.6±2.2 mmol/L), but there was not a big difference between the two groups. A total of 5 patients were diagnosed with mesenteric ischemia in the conservative oxygen group only, while no cases were detected in the liberal oxygen group [13]. Indeed, elevated lactate can be an early alarming sign of mesenteric ischemia [26].

In the current study, the percentage of patients subjected to both non-invasive ventilation and MV was higher in group B

(17.8% and 25%) than in group A (7.2% and 14.3%), but there was no statistically significant difference between them. Also, 25% of group A patients *versus* 14.3% of group B patients stayed on MV for more than 10 days without significant difference between them. These results were non-significant among both currently studied groups due to the small sample size included in both groups and may be due to the fact that all the studied patients had non-severe ARDS (PaO_2/FiO_2 ratio greater than 100) and could tolerate either oxygen target strategies. Martin and Grocott [16] stated that patients with subacute hypoxemia (decreased arterial oxygen within 6 hours to 7 days) as in pneumonia or sustained hypoxemia (decreased arterial oxygen for 7 to 90 days) and prolonged ARDS have sufficient time to be adapted and can tolerate a permissive hypoxemia strategy, which may ameliorate the patient outcomes; however, normalization of arterial oxygen for those patients may be potentially harmful. Similarly, Barrot *et al*. [13] and Schjorring *et al*. [11] found that the use of non-invasive ventilation, or MV, was similar in the studied groups.

Contrary to our study, Panwar *et al*. [12] noticed a lower mandatory MV mode use in the conservative oxygenation group (SpO_2 target 88-92%) than in the conventional group (SpO_2 target ≥96%), which might indicate that lower FiO_2 needs by the conservative patient group allowed for early weaning attempts. The conservative arm spent more time with hypoxemia, while the liberal arm spent more time with hyperoxia. Indirect evidence suggests that permissive hypoxemia might reduce the potential dose-dependent side effects of traditional liberal oxygen therapy and hence improve outcomes in some patient groups [7]. However, there is no accurate threshold for permissive hypoxemia [17].

Girardis *et al*. observed that patients in the conservative group (target PaO_2 between 70 and 100 mmHg or SpO_2 between 94 and 98%) showed significantly more MV-free hours (p=0.02) and a significant reduction in ICU mortality (p=0.01) [19]. When compared with patients in the conventional group (PaO_2 up to 150 mmHg or SpO_2 between 97 and 100%), the high oxygen supply in the latter group may delay the recovery or deteriorate the underlying lung pathology.

The present study provided better outcomes associated with group A than group B regarding the percent of dead patients (21.4% *versus* 35.7%), respectively, but no significant difference between groups. In concordance with our result, Schjørring *et al*. (a randomized study including adult ICU patients with acute type I respiratory failure) found that maintaining a PaO_2 of 60 mmHg instead of a PaO_2 of 90 mmHg did not lead to better outcomes such as the number of deaths, MV-free days, the percentage of survival days after hospital discharge, and serious complications at 90 days [11]. However, the later study results do not conclude that applying a lower oxygen therapy strategy has either harmful or beneficial effects on critically ill patients.

In the trial by Barrot *et al*. [13], as regards the 28-day mortality, no statistically significant difference was detected between patients' groups, but there was significantly higher 90-day mortality in the lower oxygenation group. Moreover, Chen *et al*. found that ICU patients with PaO_2/FiO_2 greater than 100 mmHg who received conservative oxygen therapy showed significantly lower mortality (p=0.01) [18].

Our study showed that the mean survival duration overall was 23.76±2.58 days: in group A, it was 24.45±2.58 days, and in group B, it was 23.50±2.27 days. This finding agreed with that of Panwar *et al.,* who showed survival analysis curves were similar in both treatment groups [12].

Previous studies provide inadequate support for the safety of a conservative oxygen strategy (SpO_2 88-92%) in mechanically ventilated patients [25,27]. Also, the safe upper limit for SpO_2 in the conventional oxygen strategy is undetermined. Thus, many future studies might apply a closed-loop feedback system that allows using titrated FiO_2 that is nearer to the SpO_2 target range, thus guarding against the hazards of excess undesired oxygen therapy [17,28].

Another recently published meta-analysis by Zhao *et al*. investigated different oxygenation goals in mechanically ventilated patients with triad classification [29]: conservative (PaO_2 from 55 to 90 mmHg), moderate (PaO_2 from 90 to 150 mmHg), and liberal (PaO_2 more than 150 mmHg) and tetrad classification, which subdivided the conservative group from the triad classification into far-conservative (PaO_2 from 55 to 70 mmHg) and conservative (PaO_2 from 70 to 90 mmHg) subgroups. In the triad classification, the moderate and conservative groups had statistically matched results, and both showed lower mortality than the liberal group. The tetrad classification also suggested that the moderate and conservative groups showed lower mortality than the far more conservative and liberal groups. So, in MV patients, various oxygenation targets may not cause different mortalities. The favorite outcome of keeping the PaO_2 range between 70 and 150 mmHg should be validated soon.

Limitations

The limitations of this study are the small sample size and the lack of follow-up for a longer duration (more than 30 days).

Conclusions

In RICU, there was no difference in outcome between conservative and conventional oxygen therapy. Conservative oxygen therapy may be applied safely to acute type I respiratory failure patients. Despite that, there is a lack of strong evidence supporting the application of this modality in the management of such cases.

Recommendation

Further multicenter studies with larger sample sizes are needed to study "normal" *versus* "low" oxygenation strategies for hypoxemic respiratory failure patients, as until now, only a few studies were concerned with this research aspect.

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