The effects of oxygen in critical illness

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EFFECTIVENESS AND CLINICAL OUTCOMES OF A TWO-STEP IMPLEMENTATION OF CONSERVATIVE OXYGENATION TARGETS IN CRITICALLY ILL PATIENTS: A BEFORE AND AFTER TRIAL

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ABSTRACT

Objective

Conservative oxygen therapy is aimed at the prevention of harm by iatrogenic hyperoxia while preserving adequate tissue oxygenation. Our aim was to study the effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in the ICU.

Design

This was a before and after stepwise implementation study of conservative oxygenation targets, between July 2011 and July 2014. The primary endpoint was the proportion of PaO_2 values within the target range. Secondary outcomes included ventilator-free days (VFDs) at day 28, length of stay (LOS), and mortality.

Setting

Three closed-format ICUs in the Netherlands.

Patients

We analysed data on 15,045 eligible admissions.

Interventions

The first implementation phase consisted of providing training and feedback on new guidelines instructing for explicit targets for arterial oxygen tension (PaO_2 55–86 mmHg) and oxyhemoglobin saturation (SpO_2 92–95%). In the second phase, bedside clinicians were additionally assisted in guideline adherence by a computerized decision-support system.

Measurements and Main Results

The proportion of PaO_2 in the target range increased from 47% at baseline to 63% in phase 1 and to 68% in phase 2 ($P<0.0001$). Episodes of hyperoxia decreased ($P<0.0001$), whereas hypoxic episodes remained unchanged ($P=0.06$) during the study. Mechanical ventilation time was significantly lower ($P<0.01$) during both study phases. After adjustment for potential confounders, VFDs in phase 1 and phase 2 were higher than baseline: adjusted mean difference 0.55 [95% CI 0.25, 0.84] and 0.48 [0.11, 0.86], respectively. Adjusted ICU mortality and intensive care unit free-days did not significantly differ between study phases. Hospital mortality decreased in reference to baseline: adjusted OR 0.84 [95% CI 0.74, 0.96] for phase 1 and 0.82 [95% CI 0.69, 0.96] for phase 2.

Conclusions

Stepwise implementation of conservative oxygenation targets was feasible, effective, and appeared safe in critically ill patients. The implementation was associated with several changes in clinical outcomes, but the causal impact of conservative oxygenation is still to be determined.

Trial registration: Netherlands Trial Register, number NTR3424

INTRODUCTION

The application of oxygen has always been of undisputed importance in emergency and critical care medicine. It is a highly effective therapy in preventing or compensating hypoxic injury and has life-saving properties. However, the risks of excessive oxygenation have recently placed the liberal use of oxygen in a new perspective. Oxygen is essential for cell metabolism and organ function, but triggers free radical formation and induces hemodynamic and inflammatory changes in higher doses (1-4). Furthermore, hyperoxia may promote lung injury during mechanical ventilation and has been linked to poor outcome in various subgroups (5-10). A considerable proportion of patients in the intensive care unit (ICU) is exposed to hyperoxia (11, 12), but preventive strategies may be hampered by a lack of clinical trials. Guidelines are available for a limited number of subgroups and are not easily extrapolated to universal recommendations for critically ill patients.

Conservative oxygen therapy is aimed at the prevention of iatrogenic hyperoxia while preserving adequate tissue oxygenation through careful oxygen titration (13, 14). This pragmatic strategy is increasingly advocated but its feasibility and effects on important clinical parameters are still to be assessed (15, 16). We hypothesized that a stricter adherence to conservative oxygenation guidelines may improve patient-centered outcomes by preventing derangements and inherent harm. Our aim was to study the effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in the ICU.

MATERIALS AND METHODS

Study Design

This was a before and after stepwise implementation study of conservative oxygenation targets in the ICUs of three participating hospitals, including two academic and one large teaching hospital in the Netherlands. The participating ICUs are mixed medical and surgical, tertiary care units, with 20–30 beds, where full responsibility for the patient and treatment is transferred to the critical care physician.

The study was registered with the Netherlands Trial Register, number NTR3424. Ethical approval was granted by the Medical Ethical Committee of the Leiden University Medical Center. The need for informed consent was waived under Dutch National law for the type of study and in view of the retrospective and anonymous data collection.

Data Collection

Arterial blood gas (ABG) analyses, concurrent ventilator settings, and hourly pulse oximetry data recorded between July 1, 2011 and July 1, 2014 were extracted from the patient data management system (PDMS) databases (MetaVision, iMDsoft, Tel Aviv, Israel) of participating ICUs. Data were supplemented with anonymous demographic patient data, admission and discharge data, and data to quantify severity of illness from the Dutch National Intensive Care Evaluation (NICE) registry, a high quality database, which is subject to multiple quality checks and local audits in accordance with applicable research and ethical protocols (17).

All ABG data were used when analyzing the effects on oxygenation. For clinical endpoints, data were summarized per patient admission and in case of readmissions only the first admission was included. Analyses were conducted on data from all ICU patients with subgroup analyses on mechanically ventilated patients. Patients on extracorporeal membrane oxygenation were excluded from the study. Retrospective baseline analyses were performed over a 12-months period prior to the implementation and details have been described previously (11).

Procedures

At baseline, oxygen therapy was approached liberally and targets for the partial pressure of arterial oxygen (PaO_2) only specified a lower limit of 75 mmHg with liberal oxyhemoglobin saturation by pulse oximetry (SpO_2), in the participating hospitals. Local guidelines instructed for a fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP) depending on individual oxygenation measures and generally avoiding FiO_2 levels higher than 0.6 by increasing PEEP levels, instituting inverse-ratio ventilation, or prone positioning.

The first implementation phase of this study started at July 2012 and consisted of providing a written guideline, instructing to supply as little oxygen as possible with clear recommendations how to adapt oxygen administration and ventilator settings depending on ABG analyses. Guidelines were available as pocket cards, on posters, and electronically in participating hospitals. The study PaO_2 and SpO_2 targets were set between 55 and 86 mmHg, and 92–95%, respectively, and were chosen since they were considered safe, feasible, and consistent with previously suggested targets (18, 19). In patients with severe cardiac ischemia, cerebral ischemia, or untreatable anemia, higher target levels up to 105 mmHg were allowed. Repeated passive and interactive education on the rationale of conservative oxygenation targets and a clear description of preferred PEEP/FiO_2 combinations were provided to all ICU clinicians in the participating hospitals. Baseline strategies for protective ventilation remained unchanged and during all study phases guidelines instructed for tidal volumes between 6–8 ml/kg ideal body weight, PEEP levels between 5–24 cm H_2O, respiratory rate between 8–35 per minute and pH higher than 7.2. During the first study phase feedback was provided by statistical process control (SPC) and involvement of local leadership to promote a culture that supports guideline compliance. SPC was provided through newsletters and posters showing a summary of the guideline and the results of the previous time period including plots with mean and confidence interval statistics per week for oxygenation in range, PaO_2, SpO_2, FiO_2, and PEEP.

In the second and last phase of this study, from December 2013 till July 2014, a computerized decision-support system (CDSS) was introduced in the active, critiquing mode, meaning that it will automatically give decision-support, but only if the actual situation is not according to the guideline provided in phase 1 (20, 21). Raw data of all registered measurements were used for CDSS and filtered on data quality. A pop-up window appeared in the PDMS for bedside clinicians if either PaO_2 in ABG analysis was higher than the upper level or SpO_2 measurements were continuously higher than or equal to 97% for at least 30 minutes. The event was only triggered if the FiO_2 or PEEP level was not lowered within 40 minutes after registration of out-of-range oxygenation and

the previous notification was more than three hours ago. The notification window suggested to adjust oxygen administration and/or ventilator settings for a maximum of two times per shift and not within the first three hours of ICU admission. Measures from the first phase of implementation were also continued using repeated training and feedback. The implemented guidelines and CDSS were introduced with an intention-to-treat approach. Actual decisions to change the settings or targets were left to the discretion of the attending physicians and nurses in the ICU.

Outcomes

The primary endpoint was a priori defined as the proportion of PaO_2 values within the targeted study range. Secondary outcomes included ventilator-free days at day 28 after admission, duration of mechanical ventilation, length of stay (LOS), and mortality. PaO_2 according to study protocol was defined as 1) any PaO_2 in target range; 2) any PaO_2 higher than target range with concurrent FiO_2 at 0.21 and PEEP at 5 or followed by a decrease in FiO_2 or PEEP; 3) any PaO_2 lower than target range with concurrent FiO_2 at 1.0 and PEEP at 24 or followed by an increase in FiO_2 or PEEP. Hyperoxia was defined as any PaO_2 higher than 120 mmHg (22, 23) and hypoxia as any PaO_2 lower than 45 mmHg.

Mechanical ventilation time was calculated as the sum of all mechanically ventilated episodes during the same admission. The ventilator-free days (VFDs) were calculated as the number of ventilator-free days and alive, 28 days after ICU admission according to a previously described definition (24). Accordingly, the intensive care unit-free days (ICUFDs) were calculated as the number of days not spent in the ICU and alive at day 28. Oxygenation index was calculated as the FiO_2/PaO_2 ratio multiplied by the concurrent mean airway pressure. The standardized mortality ratio (SMR) was calculated using the APACHE IV predicted mortality.

Statistical Analysis

The study was designed to detect a 5% difference in the primary endpoint with 98% power, assuming 5000 ICU admissions in the participating hospitals per year.

Every set of ABG data and ventilator settings could be compared with the following set, as described previously (11, 25). Means with standard deviations and medians with interquartile ranges are provided according to the underlying distribution. In some cases, both means and medians are provided in order to comprehensively summarize the data. Differences between study phases were tested with ANOVA or Kruskal Wallis as appropriate. Multivariate analyses were performed using generalized linear regression models for ventilator-free and ICU-free days and logistic regression for mortality while adjusting for confounding covariates. Confounding variables were stepwise selected using the 10% change-in-estimate method (26). Propensity scores were included in the multivariate models in order to adjust for each patient's propensity to be admitted during either study phase. Variables included in the propensity score model were age, sex, hospital, APACHE III score, admission type, admission source, planned admission, co-morbidities, vaso-active drugs in the first 24 hours of admission and confirmed infection within 24 hours of admission. Mixed-effects models with random intercepts were performed to account for random effects within patients or hospitals. Inspection of the variance inflation factors indicated absence of important

multicollinearity in the multivariate models. All analyses were conducted using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 0.98.1103 (RStudio Inc, Boston, MA).

RESULTS

In total, 295,701 ABG analyses were obtained over the baseline and implementation period. After excluding readmissions, 15,045 patients were included (Table 1). Eligible patients were predominantly male (64.2%), with a median age of 65 years. The majority of patients were mechanically ventilated at any time (81.8%) during admission and 17.3% was ventilated for more than 48 hours. Patient characteristics were comparable across study phases in terms of age, sex, body mass index, planned admission rate, illness severity, and several co-morbidities. The percentage of medical admissions increased from 33.7% at baseline to 36.8% in phase 1 and 38.1% in phase 2.

During the study, median levels of arterial oxygen pressures (PaO_2), oxyhemoglobin saturation (SpO_2) and central venous oxygen saturation ($ScvO_2$) decreased significantly (Table 1). Lactate was slightly higher during phase 2, but not during phase 1.

Arterial oxygenation

The proportion of ABG analyses with a PaO_2 in the targeted study range was markedly higher after implementation and increased from 47% during baseline to 63% in the first implementation phase and 68% during the second implementation phase (Table 2).

The mean difference between baseline and phase 1 was 16.1 [95% CI 15.8, 16.5] and 21.0 [95% CI 20.5, 21.5] between baseline and phase 2. The compliance showed a gradual increase during the 12 months of phase 1, but in comparison to the end of phase 1 no further improvement was found after implementation of the CDSS in phase 2 (Fig. 1).

The proportion of PaO_2 in range per patient admission, increased from 38% at baseline to 53% in phase 1 and 57% in phase 2. PaO_2 within target range as well as PaO_2 outside target range but promptly followed by adequate adjustments of oxygen administration or ventilator settings (PaO_2 according to study protocol) increased from 72% to 86% and 90%, respectively. The proportion of SpO_2 measurements in the target range increased from 16% to 25% and 27%, respectively. PaO_2 levels showed a rapid and persistent decline after the study start (supplemental figures, Supplemental Digital Content 1). The incidence of hyperoxia decreased from 15.3% during baseline to 9.0% and 7.6% in phase 1 and phase 2, respectively. The incidence of hypoxic episodes (<45 mmHg) did not essentially change (0.4% during baseline, 0.5% during both implementation phases).

In mechanically ventilated patients, the oxygenation index and FiO_2 levels decreased significantly during the study, along with an increase in PaO_2/FiO_2 ratio (Table 1). PEEP levels increased marginally in phase 2, and were adjusted less frequently than FiO_2 levels in all study phases. Mean airway pressures remained unchanged. Oxygenation higher than the upper study limit was less commonly observed after implementation and FiO_2 and PEEP levels were more frequently lowered in these cases (Table 2). Likewise, these ventilator settings were more frequently increased when PaO_2 levels were lower than the lower study limit.

Table 1. Descriptive characteristics

	All patients	Study phase			
		Baseline	Phase 1	Phase 2	P-value
Patient characteristics					
No. of patients	15,045	4,890	7,148	3,007	-
Demographics					
Age, years	65 (54-73)	65 (54-73)	65 (54-73)	65 (55-73)	0.60
Male, n	9665 (64.2%)	3171 (64.8%)	4595 (64.3%)	1899 (63.2%)	0.31
BMI, kg/m^2	25.8 (23.3-29.0)	25.7 (23.2-29.0)	25.8 (23.4-29.0)	26.0 (23.4-29.1)	0.22
Planned admission, n	7562 (50.3%)	2452 (50.1%)	3600 (50.4%)	1510 (50.2%)	0.97
Medical admission, n	5422 (36.0%)	1648 (33.7%)	2628 (36.8%)	1146 (38.1%)	<0.0001
Chronic health condition					
Acute renal failure, n	1105 (7.3%)	323 (6.6%)	547 (7.7%)	235 (7.8%)	0.05
Cancer, n	665 (4.4%)	206 (4.2%)	308 (4.3%)	151 (5.0%)	0.19
Cardiovascular disease, n	938 (6.2%)	308 (6.3%)	400 (5.6%)	230 (7.6%)	0.0005
Cirrhosis, n	277 (1.8%)	83 (1.7%)	118 (1.7%)	76 (2.5%)	0.01
COPD, n	1074 (7.1%)	313 (6.4%)	529 (7.4%)	232 (7.7%)	0.04
Diabetes, n	2609 (17.3%)	824 (16.9%)	1236 (17.3%)	549 (18.3%)	0.27
Renal disease, n	775 (5.2%)	231 (4.7%)	365 (5.1%)	179 (6.0%)	0.05
Respiratory disease, n	429 (2.9%)	160 (3.3%)	210 (2.9%)	59 (2.0%)	0.003
Severity of illness					
APACHE III score	53 (40-74)	53 (40-75)	54 (41-74)	53 (40-73)	0.42
APACHE IV predicted mortality, %	5.2 (1.4-22.5)	5.0 (1.3-22.9)	5.3 (1.5-22.2)	5.2 (1.5-22.3)	0.39
SAPS II score	34 (26-45)	34 (26-45)	34 (26-45)	34 (26-44)	0.29
SAPS II predicted mortality, %	15 (7-34)	15 (7-34)	15 (7-34)	15 (7-32)	0.28
Oxygenation and ventilation characteristics					
Arterial blood gas analyses, n	295,701	106258	137506	51937	-
PaO_2, mmHg	81 (70-98)	87 (74-107)	78 (68-93)	76 (67-89)	<0.0001
$PaCO_2$, mmHg	40 (35-46)	40 (35-46)	40 (35-47)	39 (34-45)	<0.0001
pH	7.42 (7.36-7.47)	7.41 (7.35-7.46)	7.42 (7.36-7.47)	7.43 (7.37-7.48)	<0.0001

Table 1. (continued)

		Study phase			
	All patients	**Baseline**	**Phase 1**	**Phase 2**	**P-value**
Hb, mmol/L	6.2 (1.2)	6.2 (1.2)	6.3 (1.2)	6.2 (1.3)	<0.0001
Lactate, mmol/L	1.5 (1.0-2.2)	1.5 (1.0-2.1)	1.4 (1.0-2.1)	1.6 (1.2-2.4)	<0.0001
Glucose, mmol/L[a]	7.6 (6.4-9.1)	7.5 (6.4-8.9)	7.6 (6.5-9.1)	7.8 (6.6-9.4)	<0.0001
Hourly pulse oximetry measurements, n	1,382,882	449,176	660,778	272,922	-
SpO_2, %	97 (95-99)	98 (96-100)	97 (94-99)	96 (94-98)	<0.0001
Venous blood gas analyses, n	17,753	4,817	8,811	4,125	-
$ScvO_2$, %	63.1 (10.4)	63.7 (10.7)	63.0 (10.4)	62.7 (10.2)	<0.0001
Ventilator settings					
FiO_2[c]	0.40 (0.31-0.50)	0.40 (0.40-0.50)	0.40 (0.30-0.45)	0.35 (0.30-0.45)	<0.0001
PEEP, cm H_2O[c]	7 (5-10)	7 (5-10)	7 (5-10)	8 (5-10)	<0.0001
Mean airway pressure, cm H_2O[b]	11 (9-14)	11 (9-14)	11 (9-14)	11 (9-14)	0.42
Oxygenation measures					
PaO_2/FiO_2 ratio	219 (165-291)	216 (164-285)	220 (165-291)	227 (168-300)	<0.0001
Oxygenation index[b]	3.8 (2.5-6.1)	3.9 (2.5-6.3)	3.8 (2.5-6.0)	3.7 (2.5-5.9)	<0.0001

Data are means (standard deviation), or medians (interquartile range) according to distribution, unless stated otherwise. Group comparisons between study phases were tested by ANOVA or Kruskal Wallis test according to distribution. Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; Hb, hemoglobin; SpO_2, oxyhemoglobin saturation; $ScvO_2$, central venous oxygen saturation; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure. [a] Glucose measurement from the ABG or closest to the time registration of the ABG was included, using a grace period of 10 minutes before or after ABG sampling. [b] Mean airway pressure and oxygenation index were assessed where requisite data was available (n=56,934). [c] FiO_2, PEEP is summarized data of ventilator settings at the time points of the concurrent ABG analyses measured during mechanical ventilation (n=186,513).

Table 2. Measures of implementation and oxygenation during all study phases

	Total	Study phase			
		Baseline	Phase 1	Phase 2	P-value
PaO_2 in target range, %	57.9	46.7	62.8	67.7	<0.0001
SpO_2 in target range, %	22.2	16.0	24.6	26.6	<0.0001
PaO_2 in target range per patient, %	48.6	38.0	52.5	56.8	<0.0001
PaO_2 according to study protocol, %	81.8	72.2	85.9	89.5	<0.0001
PaO_2 > upper study limit, %	39.4	51.3	34.1	29.0	<0.0001
of which followed by decrease in FiO_2 or PEEP, %[a]	*45.7*	*39.6*	*50.3*	*55.9*	*<0.0001*
PaO_2 < lower study limit, %	2.8	2.0	3.2	3.3	<0.0001
of which followed by increase in FiO_2 or PEEP, %[a]	*56.4*	*52.4*	*55.0*	*66.6*	*<0.0001*
PaO_2 > 120 mmHg, %	11.0	15.3	9.0	7.6	<0.0001
PaO_2 < 45 mmHg, %	0.4	0.4	0.5	0.5	0.06
ABG per patient, n	7 (4-16)	7 (4-17)	6 (4-16)	6 (4-15)	<0.0001
ABG per 24 hours, n	5 (4-6)	5 (4-7)	5 (4-6)	4 (3-6)	<0.0001

Abbreviations: ABG, arterial blood gas; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SpO_2, oxyhemoglobin saturation by pulse oximetry.
[a]Data in italics are subanalyses on mechanically ventilated patients of which PaO_2 was higher than the upper limit or lower than the lower limit.

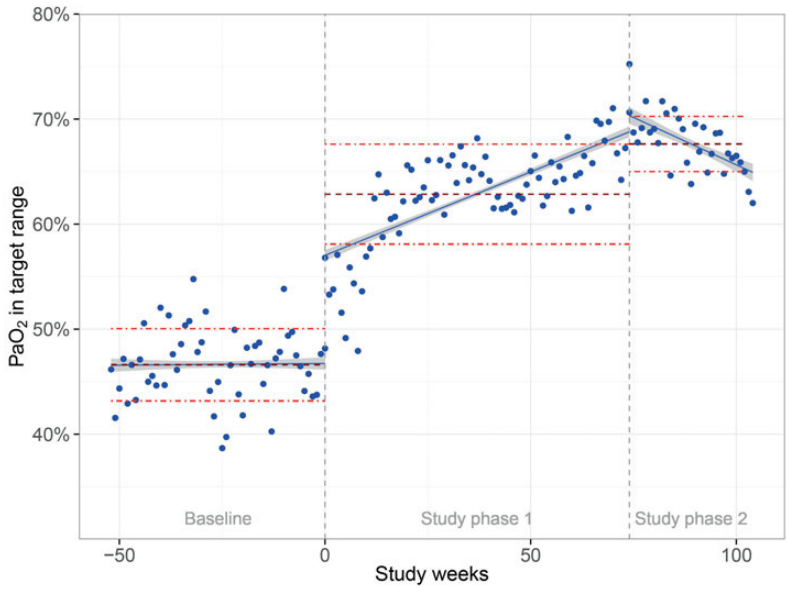

Figure 1. Percentage of arterial blood gas analyses in targeted oxygenation range during baseline and study phases.
Blue scatters are weekly means of primary outcome with weighted regression lines (95% CI) per study phase. Red horizontal lines are study phase means with SD

Table 3. Crude clinical outcomes during all study phases

		Study phase			
	Total	**Baseline**	**Phase 1**	**Phase 2**	**P-value**
All patients, n	15045	4890	7148	3007	-
ICU LOS					
Mean, days	3.4 (6.5)	3.4 (6.8)	3.5 (6.5)	3.4 (5.9)	0.72
Median, days	1.4 (0.8-3.1)	1.1 (0.8-3.0)	1.5 (0.8-3.2)	1.7 (0.9-3.6)	<0.0001
Hospital LOS					
Mean, days	14.3 (17.1)	14.7 (18.0)	14.2 (17.1)	13.8 (15.5)	0.04
Median, days	9 (6-16)	9 (6-16)	9 (6-16)	8 (5-16)	0.22
ICUFDs, days	21.6 (9.2)	21.5 (9.5)	21.7 (9.1)	21.6 (8.9)	0.63
ICU mortality, n	1487 (9.9%)	475 (9.7%)	709 (9.9%)	303 (10.1%)	0.86
Hospital mortality, n	2063 (13.7%)	723 (14.8%)	942 (13.2%)	398 (13.2%)	0.03
SMR [95% CI]	0.78 [0.75, 0.82]	0.84 [0.77, 0.90]	0.75 [0.70, 0.80]	0.76 [0.69, 0.84]	0.01
Mechanically ventilated at any time, n	12206 (81.1%)	4043 (82.7%)	5789 (81.0%)	2374 (78.9%)	0.0003
Mechanical ventilation time					
Mean, hours	46.9 (111.4)	50.7 (129.8)	46.0 (103.9)	42.5 (93.7)	0.01
Median, hours	10.8 (5.2-39.0)	11.4 (6.0-40.3)	10.8 (5.0-38.8)	9.4 (4.6-36.4)	<0.0001
ICU LOS					
Mean, days	3.8 (7.1)	3.8 (7.4)	3.9 (7.1)	3.8 (6.5)	0.63
Median, days	1.7 (0.9-3.8)	1.3 (0.8-3.6)	1.7 (0.9-3.8)	1.8 (0.9-4.0)	<0.0001
Hospital LOS, days					
Mean, days	14.3 (17.2)	14.7 (18)	14.3 (17.3)	13.7 (15.7)	0.09
Median, days	9 (6-16)	9 (6-16)	9 (6-16)	8 (6-15)	0.22
VFDs, days	22.3 (9.4)	22.1 (9.6)	22.5 (9.3)	22.5 (9.3)	0.10
ICUFDs, days	21.1 (9.6)	21.0 (9.8)	21.1 (9.5)	21.0 (9.4)	0.78
ICU mortality, n	1393 (11.4%)	452 (11.2%)	663 (11.5%)	278 (11.7%)	0.80
Hospital mortality, n	1802 (14.8%)	634 (15.7%)	824 (14.2%)	344 (14.5%)	0.13
SMR [95% CI]	0.80 [0.76, 0.84]	0.85 [0.78, 0.91]	0.77 [0.71, 0.82]	0.80 [0.71, 0.88]	0.01

Data are means (standard deviation), or medians (interquartile range) according to distribution, unless stated otherwise. Abbreviations: ICU, intensive care unit; LOS, length of stay; ICUFDs, intensive care unit-free days and alive at day 28; VFDs, ventilator-free days and alive at day 28; SMR, standardized mortality ratio according to APACHE IV model.

Secondary end points

Secondary outcome measures are listed in Table 3 and depicted in the supplemental figures.

ICU mortality and ICUFDs did not differ between study phases. The median ICU LOS was longer in phase 2 compared to phase 1 and baseline, whereas the mean ICU LOS remained unchanged. Median hospital LOS did not change and hospital mortality decreased from 14.8% during baseline to 13.2% during both implementation phases. Standardized mortality ratios and Kaplan-Meier curves for survival and mechanical ventilation time are shown in more detail in the supplemental figures.

For patients requiring mechanical ventilation at any time (n=12,206), median mechanical ventilation time decreased from 11.4 hours at baseline to 10.8 in phase 1 and 9.4 hours in phase 2.

Mortality rates showed no statistically significant change in this subgroup. The VFDs increased from 22.1 to 22.5 days after implementation. For the smaller cohort of patients who were ventilated for more than 48 hours (n=2,609), no significant differences for major outcome measures between study phases were observed (Supplemental Tables, Supplemental Digital Content 2). For surviving patients, mechanical ventilation time decreased, ICU LOS increased, whereas hospital LOS remained unchanged over the study time (Supplemental Tables, Supplemental Digital Content 2).

Separate analyses for the effect of the implementation in the individual participating ICUs are shown in the supplemental tables. Similar improvements in PaO_2 in target range were found in each ICU. In one of the units, the proportion of medical admissions increased markedly in phase 1 and phase 2, and potentially related to this, a concurrent increase in ICU LOS was found. The effect sizes of other outcome measures were in the same order of magnitude for all three ICUs.

Multivariate analyses

When the model for the proportion of PaO_2 samples in the target range was reanalysed in mixed-effects models, the associations were virtually unchanged (data not shown). The crude and adjusted estimates were calculated as mean differences or odds ratios per study phase in reference to baseline and were adjusted for identified confounders and propensity scores (Table 4). No increase in ICUFDs was found in either the unadjusted or adjusted analyses. After adjustment, the increase in VFDs was stronger. There were no statistically significant differences in ICU mortality, whereas the odds ratios for hospital mortality were lower in both implementation phases, after adjustment for confounders.

Table 4. Clinical outcomes with adjustment for confounders

	Study phase 1		Study phase 2	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Mean difference [95% CI]				
VFDs[a]	0.38 [0, 0.76]	0.55 [0.25, 0.84]*	0.39 [-0.08, 0.87]	0.48 [0.11, 0.86]*
ICUFDs[b]	0.16 [-0.17, 0.50]	0.16 [-0.11, 0.42]	0.08 [-0.34, 0.50]	0.10 [-0.23, 0.43]
Odds ratio [95% CI]				
ICU mortality[c]	1.02 [0.91, 1.16]	1.09 [0.93, 1.27]	1.04 [0.89, 1.21]	1.09 [0.90, 1.32]
Hospital mortality[c]	0.87 [0.79, 0.97]*	0.84 [0.74, 0.96]*	0.88 [0.77, 1.00]	0.82 [0.69, 0.96]*

Multivariate models were adjusted for admission type, APACHE III score and propensity score (for admission during either phase 1 or phase 2). Abbreviations: ICUFDs, intensive care unit-free days and alive at day 28; VFDs, ventilator-free days and alive at day 28. [a] Mean difference in ventilator-free days in reference to baseline for subgroup of mechanically ventilated patients. [b] Mean difference in intensive care unit-free days in reference to baseline for all patients. [c] Odds ratio (OR) for indicated mortality in reference to baseline for all patients. * P<0.05

DISCUSSION

Key findings

In this multicenter clinical trial, stepwise implementation of a strategy targeting conservative oxygenation levels through education, feedback, and decision support was shown to be feasible and effective in critically ill patients. Targeting PaO_2 levels of 55–86 mmHg and SpO_2 levels of 92–95% resulted in lower but safe oxygenation levels of arterial blood. Taking the before after design in consideration, this study was limited in the ability to address the clinical impact of our strategy. In adjusted analyses, implementation of the study protocol was associated with a slight improvement in ventilator-free days and hospital mortality. However, ICU-free days and ICU mortality were unaffected over the study time.

Interpretation

The proportion of PaO_2 samples in the target range (primary outcome) increased strongly in the first study phase in which traditional implementation strategies were applied. These strategies consisted of education for all ICU nurses and physicians, providing written guidelines on targets and ventilator settings, and frequent feedback using statistical process control. In contrast, the CDSS, which was offered in phase 2, had no additional effect on the primary outcome and may even have been somewhat counterproductive. However, phase 2 was shorter than phase 1 and trends could therefore be assessed with less precision. A ceiling effect of modifiable oxygenation should also be considered as ventilator settings are often initiated outside the ICU (e.g. during anesthesia or at the emergency room) and first ABG samples, taken shortly after ICU arrival, were responsible for an important part of these out-of-range samples. Other reasons for a ceiling effect can be postulated in terms of knowledge barriers, attitude barriers, and behavioral barriers (27). Barriers include reluctance of clinicians to adhere to new guidelines, resistance to change, and reluctance to replace pre-existing guidelines (28-30). Guideline implementation strategies were previously shown to be successful when strategies were multifaceted and actively engaged clinicians throughout the process (31). Although CDSS is usually beneficial (32), its effects in a multifaceted approach may be less (cost-)effective (33-35). An alternative explanation for the apparently paradoxical course of compliance in phase 2, is that traditional implementation was so successful that no additional benefit could be achieved by a decision support module. However, we cannot rule out that prolonged CDSS, different algorithms, more frequent reminders, or more specific suggestions to change ventilator settings, could have been more effective. During phase 2, the proportion of PaO_2 values within range was even somewhat lower than at the end of phase 1. Although this may be normal fluctuation by chance, decision support may alternatively induce passive behavior of bedside clinicians leading to slower adjustments of ventilator settings. Even after implementation of conservative oxygenation targets, approximately 30% of PaO_2 and 70% of SpO_2 measurements was higher than the target range. The latter marker of oxygenation is indeed less reliable and more variable, albeit the percentage of registered values increased significantly with implementation. The proportion of samples according to protocol, also including PaO_2 outside the limits followed by appropriate adjustments of oxygen and ventilator settings, was much better, reaching almost 90%

at the end of the study. In this respect, phase 2 was superior to phase 1, in line with other clinical outcome measures in multivariate analyses. Controlled evidence is warranted to further evaluate CDSS in comparison to traditional training and feedback (21).

Strengths and Limitations

The following potential limitations of this study should be considered. First, the non-randomized intervention in this clinical trial hampers causal inferences, especially regarding effects on relevant clinical patient outcomes. Differences in case-mix between the baseline period and both implementation phases may have been responsible for differences in outcomes such as length of stay, mechanical ventilation time, or hospital mortality. However, demographic characteristics and illness severity scores were very similar across the study periods and multivariate analyses were adjusted for confounders and propensity scores. The longitudinal design of this study yields potential bias as outcomes of ICU patients may improve over time due to factors other than oxygenation targets. Hypothesizing that attentive monitoring of oxygenation and ventilation improves outcome, study awareness may elicit attention bias. Indeed, we could not fully control for secular trends and potential changes in clinician behavior and ventilation management during the study. Interestingly, improvement of clinical outcomes was observed in all three ICUs during the first implementation phase, but without a further improvement after adding CDSS. Also, during the 12 months baseline period, no significant trends to improved survival, LOS, or mechanical ventilation time were found.

General oxygenation strategies were specified as much as possible, but specific and individual oxygenation strategies were left to the discretion of the participating centers and responsible clinicians. In this context, individual cases with amended target ranges including patients with severe anemia or ischemia were not specifically registered in the database. Hospital related differences in case-mix, patient care, and guideline adherence may accordingly influence the overall-effects, although there was a consistent signal for end points in the sensitivity analyses, even when wider PaO_2 target levels up to 105 mmHg were used for analysis. The only exception was ICU LOS which increased only in the ICU where an increase in the proportion of medical admissions was found. The finding that median ICU LOS increased during the study should therefore be interpreted with caution. Accordingly, in the multivariate analysis, also adjusting for admission type, no association between ICUFDs and implementation was found. Finally, our findings may not be directly generalizable to other ICUs although we believe that the inclusion of patients from three participating hospitals during two years can robustly represent a general ICU population. At least it shows the feasibility of conservative oxygen therapy with strict adherence to oxygenation targets.

Strengths of this study include the multicenter trial participation, the large patient cohort, the quality of the database, and the possibility to control for many covariates. Further, our findings are consistent with a previous single-center pilot study reporting compliance with targeted saturation in a small sample of mechanically ventilated patients (13). In this study, conservative oxygen therapy was shown to be free of adverse biochemical, physiological, and clinical outcomes. The present study confirms these findings on a larger scale and also demonstrates the feasibility of PaO_2 targets.

Clinical Implications

In mechanically ventilated patients, we could not demonstrate an improvement in mortality rates and LOS, yet mechanical ventilation time decreased in a significant manner. Potential mechanisms underlying the observed effects in clinical outcomes are multifarious. Precise control of arterial oxygenation avoids significant variation from the target range and may successfully reduce the harms associated with unnecessary extremes (15). In addition, conservative oxygen therapy may contribute to acclimatization and cellular adaptation to mild hypoxia, which may result in improved efficiency of ATP production and protection of mitochondria (15). Reducing the exposure to hyperoxia may decrease mechanical ventilation time by preventing absorption atelectasis, pulmonary inflammation, and other histopathological changes in the lung (1, 4, 9). Patient-centered outcomes are also likely to be impacted by reactive oxygen species, oxygen-induced cardiovascular alterations (2), oxidative DNA damage (36) and mediators of oxygenation. Interestingly, hospital mortality decreased during the study whereas ICU mortality remained unchanged. This observation is in agreement with results from pooled cohort studies, showing that arterial hyperoxia was associated with hospital mortality but not specifically with ICU mortality (10). Clinical improvements may alternatively be attributed to behavioral changes in clinical practice and precise control of oxygenation, rather than to the prevention of hyperoxia per se (37).

The oxygenation ranges used in this study were chosen based on previous recommendations (18, 19). In accordance, this range was within the standard of care and no reasonably foreseeable risks of the actually achieved oxygenation were anticipated. Although other target ranges for conservative oxygen therapy may well be as good as or even better than the range we studied (14), our approach was safe in terms of major clinical end points. Also, the incidence of severe hypoxia was rare and did not increase over time. In comparison to baseline, tissue oxygenation represented by arterial lactate or oxygenation index did neither deteriorate. Moreover, the higher percentiles of lactate levels remained virtually unchanged (data not shown). In prospective evaluation of conservative oxygenation, a randomized intervention, alternative mediators and the effects on specific parameters including hemodynamics and the microcirculation are still to be assessed.

CONCLUSIONS

Stepwise implementation of conservative oxygenation was feasible and showed a rapidly established high compliance to targeted arterial oxygen and saturation levels. The gradual improvement in guideline adherence was accompanied by a slight improvement in several clinical outcomes, but this should be interpreted with caution in view of the study design. Future randomized controlled studies should further clarify the causal effects of oxygenation targets on clinical outcomes for ICU patients.

DECLARATION OF INTERESTS

We declare no competing interests regarding this work. Dr. Bosman reports personal fees from consultant work for IteMedical, Dutch supplier of the PDMS, outside the submitted work. The funders

of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

ONLINE SUPPLEMENT

For the online supplements, please use the following weblinks, or scan the QR-codes with your mobile device

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REFERENCES

1. Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. Curr Opin Crit Care. 2007;13(1):73-8.
2. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J. 2009;158(3):371-7.
3. Gore A, Muralidhar M, Espey MG, Degenhardt K, Mantell LL. Hyperoxia sensing: from molecular mechanisms to significance in disease. J Immunotoxicol. 2010;7(4):239-54.
4. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. Intensive Care Med. 2015;41(6):1118-21.
5. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014;18(6):711.
6. Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation. 2014;85(9):1142-8.
7. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality. JAMA. 2010;303(21):2165-71.
8. Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS, Group PT. Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. Br J Anaesth. 2014;113 Suppl 1:i74-i81.
9. Sjoberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. J Intern Med. 2013;274(6):505-28.
10. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and Meta-Regression of Cohort Studies. Crit Care Med. 2015;43(7):1508-19.
11. Helmerhorst HJ, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Jonge E, et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. Ann Intensive Care. 2014;4(23).
12. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. J Crit Care. 2013;28(5):647-54.
13. Suzuki S, Eastwood GM, Glassford NJ, Peck L, Young H, Garcia-Alvarez M, et al. Conservative oxygen therapy in mechanically ventilated patients: a pilot before-and-after trial. Crit Care Med. 2014;42(6):1414-22.
14. Mikkelsen ME, Anderson B, Christie JD, Hopkins RO, Lanken PN. Can we optimize long-term outcomes in acute respiratory distress syndrome by targeting normoxemia? Ann Am Thorac Soc. 2014;11(4):613-8.
15. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med. 2013;41(2):423-32.
16. Gilbert-Kawai ET, Mitchell K, Martin D, Carlisle J, Grocott MP. Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients. Cochrane Database Syst Rev. 2014;5:CD009931.
17. Arts D, de Keizer N, Scheffer GJ, de Jonge E. Quality of data collected for severity of illness scores in the Dutch National Intensive Care Evaluation (NICE) registry. Intensive Care Med. 2002;28(5):656-9.
18. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351(4):327-36.
19. Patroniti N, Iotti GA. Mechanical Ventilation - skills and techniques. Patient-centered Acute Care Training (PACT) Module - European Society of Intensive Care Medicine. 2011.

20. Goud R, de Keizer NF, ter Riet G, Wyatt JC, Hasman A, Hellemans IM, et al. Effect of guideline based computerised decision support on decision making of multidisciplinary teams: cluster randomised trial in cardiac rehabilitation. BMJ. 2009;338:b1440.

21. Randolph AG, Haynes RB, Wyatt JC, Cook DJ, Guyatt GH. Users' Guides to the Medical Literature: XVIII. How to use an article evaluating the clinical impact of a computer-based clinical decision support system. JAMA. 1999;282(1):67-74.

22. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12(6):R156.

23. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med. 2012;38(1):91-8.

24. Schoenfeld DA, Bernard GR, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002;30(8):1772-7.

25. de Graaff AE, Dongelmans DA, Binnekade JM, de Jonge E. Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of FiO2. Intensive Care Med. 2011;37(1):46-51.

26. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health. 1989;79(3):340-9.

27. Rubenfeld GD. Translating clinical research into clinical practice in the intensive care unit: the central role of respiratory care. Respir Care. 2004;49(7):837-43.

28. Cahill NE, Suurdt J, Ouellette-Kuntz H, Heyland DK. Understanding adherence to guidelines in the intensive care unit: development of a comprehensive framework. JPEN J Parenter Enteral Nutr. 2010;34(6):616-24.

29. Jones NE, Suurdt J, Ouelette-Kuntz H, Heyland DK. Implementation of the Canadian Clinical Practice Guidelines for Nutrition Support: a multiple case study of barriers and enablers. Nutr Clin Pract. 2007;22(4):449-57.

30. Simpson F, Doig GS. The relative effectiveness of practice change interventions in overcoming common barriers to change: a survey of 14 hospitals with experience implementing evidence-based guidelines. J Eval Clin Pract. 2007;13(5):709-15.

31. Prior M, Guerin M, Grimmer-Somers K. The effectiveness of clinical guideline implementation strategies-a synthesis of systematic review findings. J Eval Clin Pract. 2008;14(5):888-97.

32. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. JAMA. 1998;280(15):1339-46.

33. Eslami S, Abu-Hanna A, de Jonge E, de Keizer NF. Tight glycemic control and computerized decision-support systems: a systematic review. Intensive Care Med. 2009;35(9):1505-17.

34. Eslami S, de Keizer NF, Dongelmans DA, de Jonge E, Schultz MJ, Abu-Hanna A. Effects of two different levels of computerized decision support on blood glucose regulation in critically ill patients. Int J Med Inform. 2012;81(1):53-60.

35. Eslami S, Abu-Hanna A, Schultz MJ, de Jonge E, de Keizer NF. Evaluation of consulting and critiquing decision support systems: effect on adherence to a lower tidal volume mechanical ventilation strategy. J Crit Care. 2012;27(4):425 e1-8.

36. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS, Group PT. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. Anesth Analg. 2012;115(4):849-54.

37. Eastwood GM, Peck L, Young H, Suzuki S, Garcia M, Bellomo R. Intensive care clinicians' opinion of conservative oxygen therapy (SpO_2 90-92%) for mechanically ventilated patients. Aust Crit Care. 2014;27(3):120-5.