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CONSERVATIVE OXYGEN THERAPY DURING MECHANICAL VENTILATION IN THE ICU.

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Abstract:

Background: *Patients who are going thorugh mechanical ventilation in the intensive care unit (ICU) often receive a high fraction of inspired oxygen (Fio2) and have a high arterial oxygen tension. The conservative use of oxygen may reduce oxygen exposure, diminish lung and systemic oxidative injury, and thereby increase the number of ventilator-free days (days alive and free from mechanical ventilation).*

Methods: *We randomly assigned 1000 adult patients who were anticipated to require mechanical ventilation beyond the day after recruitment in the ICU to receive conservative or usual oxygen therapy. In the two groups, the default lower limit for oxygen saturation as measured by pulse oximetry (Spo2) was 90%. In the conservativeoxygen group, the upper limit of the Spo2 alarm was set to sound when the level reached 97%, and the Fio2 was decreased to 0.21 if the Spo2 was above the acceptable lower limit. In the usual-oxygen group, there were no specific measures limiting the Fio2 or the Spo2 . The primary outcome was the number of ventilatorfree days from randomization until day 28.*

Results: *The number of ventilator-free days did not differ significantly between the conservative-oxygen group and the usual-oxygen group, with a median duration of 21.3 days (interquartile range, 0 to 26.3) and 22.1 days (interquartile range, 0 to 26.2), respectively, for an absolute difference of −0.3 days (95% confidence interval [CI], −2.1 to 1.6; P=0.80). The conservative-oxygen group spent more time in the ICU with an Fio2 of 0.21 than the usual-oxygen group, with a median duration of 29 hours (interquartile range, 5 to 78) and 1 hour (interquartile range, 0 to 17), respectively (absolute difference, 28 hours; 95% CI, 22 to 34); the conservative-oxygen group spent less time with an Spo2 exceeding 96%, with a duration of 27 hours (interquartile range, 11 to 63.5) and 49 hours (interquartile range, 22 to 112), respectively (absolute difference, 22 hours; 95% CI, 14 to 30). At 180 days, mortality was 35.7% in the conservative-oxygen group and 34.5% in the usual-oxygen group, for an unadjusted odds ratio of 1.05 (95% CI, 0.81 to 1.37).*

Conclusions: *In adults undergoing mechanical ventilation in the ICU, the use of conservative oxygen therapy, as compared with usual oxygen therapy, did not significantly affect the number of ventilator-free days.*

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INTRODUCTION:

Providing the supplemental oxygen to the patients in the intensive care unit (ICU) who are in need of invasive mechanical ventilation many times they are exposes to high fraction of inspired oxygen (Fio2) and elevated-than-normal partial pressure of arterial oxygen (Pao2) [1-3] Hyperoxemia has been strongly linked with higher mortality rate mainly among young adults who are going through mechanical ventilation [4][5]. In a meta-analysis of randomized trials including adults with acute illnesses, the use of oxygen without limitation according to achieved arterial oxygen saturation was associated with a higher rate of death than more restrictive approaches [6].

In a single-center ICU trial in which maximally two thirds of the patients were getting invasive mechanical ventilation at the time of randomization, the use of conservative oxygen therapy, a therapeutic regimen designed to minimize exposure to high levels of oxygen, was associated with a lower rate of death and a higher number of ventilator-free days than usual oxygen therapy. Since supplemental oxygen is commonly used, such findings suggest that establishing therapies for limiting oxygen use could be of value. Regardless of this need, there is a lack of good clinically directive data regarding strategies for oxygen administration in adults undergoing mechanical ventilation [7] [8] . Written informed consent for enrollment or consent to continue and to use patient data was obtained from each patient or from a legal surrogate. If a patient died before providing consent, data were included if allowed by local regulations and approved by the relevant ethics committee. The members of the writing committee vouch for the accuracy and completeness of the data and analyses, and for the fidelity of the trial to the protocol.

METHODS:

All adults (≥18 years of age) who were expected to receive mechanical ventilation in the ICU beyond the day after recruitment were eligible for inclusion in the trial. Enrollment was restricted to patients who had received less than 2 hours of invasive mechanical ventilation or noninvasive ventilation in the ICU. Eligible patients who were not enrolled within the 2-hour time window were categorized as missed, rather than excluded, for the purposes of describing the enrollment of patients. We randomly assigned patients to receive conservative oxygen therapy or usual oxygen therapy using a secure, centralized, Internet-based interface. In the two groups, the acceptable lower limit for oxygen saturation as measured by pulse oximetry (Spo2) was monitored with an alarm set at a level of 90%. This alarm limit could be altered at the discretion of the treating clinician.

If an arterial blood gas showed a Pao2 of less than 60 mm Hg or an arterial oxygen saturation (Sao2) lower than the acceptable Spo2 , the Fio2 could be increased, regardless of the Spo2 , at the discretion of the treating clinician. In the conservative-oxygen group, the Fio2 was decreased to 0.21 and supplemental oxygen was discontinued in patients who had been extubated if the Spo2 was above the acceptable lower limit. In this group, we sought to minimize exposure to an Spo2 of 97% or higher by mandating the use of an alarm that was set to sound when the Spo2 was 97% whenever supplemental oxygen was administered in the ICU. In the usual-oxygen group, there were no specific measures limiting the Fio2 or the Spo2 , and use of upper alarm limits for the Spo2 was prohibited by the protocol. In this group, the use of an Fio2 of less than 0.3 during invasive ventilation was discouraged.

In the two groups, the use of a high Fio2, regardless of the Spo2, was permitted in some specific circumstances. Other aspects of care, including ventilator weaning and extubation practices, were at the discretion of the treating clinician. Patients received the assigned oxygen-therapy strategy until discharge from the ICU or 28 days after randomization, whichever was earlier. The trial-group assignment was known to clinical staff members but was not disclosed to the patients or their families.

Outcome Measures:

The primary outcome was the number of ventilator-free days from randomization to day 28.12 ventilator-free days was defined as the total number of calendar days or portions of calendar days of unassisted breathing during the first 28 days after randomization. All the patients who had died by day 28 were considered to have had no ventilator-free days. Key secondary outcomes were death from any cause at day 90 and day 180 after randomization, the duration of survival, the proportion of patients in paid employment at baseline who were unemployed at day 180, and cognitive function and health-related quality of life at day 180. Cause-specific mortality was also recorded [11]. Cognitive function was assessed with the use of the Telephone Interview for Cognitive Status (TICS) questionnaire; scores on this questionnaire range from 0 to 41, with a higher number indicating a better outcome. Categories of cognitive function based on the TICS score were severe impairment (a score of ≤20), mild impairment

(a score of 21 to 25), ambiguous impairment (a score of 26 to 32), and no impairment (a score of >32) [12] [13].

The patients' quality of life was assessed with the use of the five-level EuroQol five dimensions (EQ-5D-5L) questionnaire; this scale evaluates mobility, personal care, usual activities, pain or discomfort, and anxiety and depression, with categorization of each of these dimensions into five levels that range from no problems to extreme problems [14] For patients with acute brain disease at randomization, we used the Extended Glasgow Outcome Scale to assess functional outcome at day 180; this scale ranges from 1 to 8, with a higher number indicating a better outcome. Centralized assessors who were unaware of trial-group assignments assessed cognitive status, quality of life, and function at day 180.

The statistical analysis plan was reported before the completion of enrollment [15]. We assumed a mean (±SD) number of 16.4±11.3 ventilator-free days in the usual-oxygen group. Allowing for a 15% inflation in the sample size to account for rank-based testing18 and an additional inflation of 80 patients to account for withdrawals and interim analyses, we determined that a sample size of 1000 patients would provide the trial with a power of 90% to detect an absolute between group difference of 2.6 ventilator-free days at day 28 after randomization with a two-sided type I error rate (alpha) of 0.05.8 All the analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization with the exception of those who had withdrawn consent for the use of their data. Missing values were not imputed. For the primary analysis, Wilcoxon rank-sum test was used with differences between medians calculated by means of quantile regression using a simplex algorithm, with the inversion method used to calculate 95% confidence intervals after adjustment for the trial site [17]. We also analyzed the primary end point using quantile regression after adjustment for site, age, sex, and risk of death, as assessed by means of the Acute Physiology and Chronic Health Evaluation (APACHE) II model and performed an unadjusted analysis [18]. We report 90-day and 180-day all-cause mortality as the proportion of patients in each treatment group, along with a risk difference and 95% confidence interval and with a corresponding odds ratio and 95% confidence interval. We compared survival times using log-rank tests and present these data as Kaplan–Meier curves and used a Cox proportional-hazards model to calculate hazard ratios for survival. (Odds ratios were calculated to describe the ratio of deaths in each treatment group and hazard ratios to describe mortality over time.) For prespecified subgroups, we performed quantile regression analysis and tested for heterogeneity between subgroups in the number of ventilator-free days by fitting an interaction between treatment and subgroup. Statistical significance was indicated by a P value of 0.05 and was determined with the use of a two-sided hypothesis test. We did not correct for multiple comparisons in the evaluation of secondary or other outcomes. Thus, such results are exploratory and are reported as point estimates with 95% confidence intervals. All the analyses were performed with the use of SAS software, version 9.4.

RESULTS:

A comparison of the characteristics of the 100 patients who were enrolled in the pilot phase of the trial and the subsequent 900 patients who were enrolled is provided in Table 2. Data regarding the primary outcome were available for the entire intention-to-treat population. The trial groups had similar characteristics at baseline. Oxygenation and Process of Care Patients in the conservative-oxygen group spent more time receiving an Fio2 level of 0.21 than those in the usual-oxygen group, for a median duration of 29 hours (interquartile range, 5 to 78) and 1 hour (interquartile range, 0 to 17), respectively (absolute difference, 28 hours; 95% confidence interval [CI], 22 to 34).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Conservative Oxygen (N=484)	Usual Oxygen (N=481)
Age — yr	58.1±16.2	57.5±16.1
Male sex — no. (%)	306 (63.2)	302 (62.8)
Source of admission to ICU — no. (%)		
Emergency department	187 (38.6)	212 (44.1)
Hospital ward	107 (22.1)	82 (17.0)
Transfer from another ICU	2 (0.4)	5 (1.0)
Transfer from a non-ICU ward of another hospital	39 (8.1)	36 (7.5)
Operating room		
After elective surgery	31 (6.4)	39 (8.1)
After emergency surgery	118 (24.4)	107 (22.2)
Median hr from initiation of invasive ventilation to randomization (IQR)†	3.2 (1.6–5.4)	3.0 (1.5–5.3)
APACHE II score‡	23.6±9.3	23.3±9.4
Diagnosis subgroup		
Admitted after surgery — no. (%)	149 (30.8)	146 (30.4)
Acute brain disease — no. (%)	199 (41.1)	184 (38.3)
Pao_2:Fio_2 ratio of <300 — no./total no. (%)	304/461 (65.9)	319/448 (71.2)
Suspected hypoxic–ischemic encephalopathy — no. (%)	87 (18.0)	79 (16.4)
Physiological features and support§		
Spo_2 — %	97.1±3.1	96.7±3.7
Median Pao_2 (IQR) — mm Hg	110 (83–177)	112 (82–167)
Pao_2:Fio_2 ratio	259±146	245±138
Median PEEP (IQR) — cm of water	6 (5–10)	6 (5–10)

The conservative oxygen group also spent less time with an Spo2 of 97% or higher than the usual-oxygen group, with a median duration of 27 hours (interquartile range, 11 to 63.5) and 49 hours (interquartile range, 22 to 112), respectively (absolute difference, 22 hours; 95% CI, 14 to 30). The number and percentage of hours with a Spo2 of less than 91% and with Spo2 of less than 88% were similar in the two groups. The mean Fio2 during the first 10 days of mechanical ventilation in the ICU and the lowest and highest Fio2 values until day 28 are provided in Figure S1. Similarly, time-weighted mean Pao2 values during the first 10 days of mechanical ventilation in the ICU and the lowest and highest Pao2 values until day 28 are provided in Figure S2. For these sets of measures, all the Fio2 and Pao2 values were lower in the conservative-oxygen group than in the usual-oxygen group.

Table 2. Primary Outcome and Key Secondary Outcomes and Process Measures.*

	Conservative Oxygen (N=484)	Usual Oxygen (N=481)	Between-Group Difference†	Unadjusted Odds Ratio (95% CI)
Primary outcome				
No. of ventilator-free days				
Median (IQR)	21.3 (0.0 to 26.3)	22.1 (0.0 to 26.2)	−0.3 (−2.1 to 1.6)‡	
Mean	15.5±11.8	16.0±11.5	−0.4 (−1.9 to 1.0)	
No. of days of ventilation among survivors — geometric mean (95% CI)	2.95 (2.61 to 3.33)	3.11 (2.76 to 3.51)	0.94 (0.80 to 1.11)	
Key secondary outcomes				
Death — no./total no. (%)§				
Day 90	166/479 (34.7)	156/480 (32.5)		1.10 (0.84 to 1.44)
Day 180	170/476 (35.7)	164/475 (34.5)		1.05 (0.81 to 1.37)
Process measures				
Median no. of hr from randomization to ICU discharge (IQR)	115 (58 to 231)	124 (63 to 252)	−8.4 (−27.7 to 10.9)	
Median no. of hr from randomization to hospital discharge (IQR)	298 (144 to 570)	314 (155 to 618)	−15.6 (−67.1 to 35.9)	
Median no. of vasopressor-free days (IQR)	23 (0 to 26)	23 (0 to 26)	0 (−0.5 to 0.5)	
Patients with RRT in ICU — no. (%)	94 (19.4)	108 (22.5)		0.83 (0.61 to 1.14)
Patients with tracheostomy in ICU — no. (%)	48 (9.9)	56 (11.6)		0.84 (0.56 to 1.26)

Primary Outcome:

At day 28, there was no significant between group difference in the number of ventilator-free days, with a median of 21.3 days (interquartile range, 0 to 26.3) in the conservative-oxygen group and 22.1 days (interquartile range, 0 to 26.2) in the usual-oxygen group (absolute difference, −0.3 days; 95% CI, −2.1 to 1.6; P=0.80).

Secondary Outcomes:

The analyses of secondary outcomes were performed a median of 186 days (interquartile range, 181 to 197 days) after randomization. By day 180, deaths were reported for 170 of 476 patients (35.7%) in the conservative-oxygen group and 164 of 475 patients (34.5%) in the usual oxygen group (unadjusted odds ratio, 1.05; 95% CI, 0.81 to 1.37; hazard ratio, 1.05; 95% CI, 0.85 to 1.30). Among the survivors, we found no evidence of a between-group difference in employment status among the patients who had been receiving pay for work at baseline, with paid employment reported in 77 of 112 patients (68.8%) in the conservative-oxygen group and in 66 of 108 (61.1%) in the usual-oxygen group. Cognitive function was similar in the two groups, with severe cognitive impairment reported in 5 of 203 patients (2.5%) in the conservative-oxygen group and in 6 of 206 (2.9%) in the usual-oxygen group. With respect to the mobility and personal-care components of the quality-of life assessment, the patients in the conservative oxygen group had a greater frequency of moderate problems and a lower frequency of severe problems than those in the usual-oxygen group. We found no evidence of differences in other domains of the quality-of-life assessment. There was substantial heterogeneity in the effect of conservative oxygen therapy on the number of ventilator-free days in patients with suspected hypoxic–ischemic encephalopathy but not in other prespecified subgroups. At day 28, among the patients with suspected hypoxic– ischemic encephalopathy, the median number of ventilator-free days was 21.1 (interquartile range, 0 to 26.1) in the conservative-oxygen group and none (interquartile range, 0 to 26)

in the usual oxygen group (absolute difference, 21.1 days; 95% CI, 10.4 to 28.0). In post hoc analyses of the subgroup with suspected hypoxic–ischemic encephalopathy performed at 180 days, death was reported in 37 of 86 patients (43%) in the conservative-oxygen group and in 46 of 78 (59%) in the usual-oxygen group (relative risk, 0.73; 95% CI, 0.54 to 0.99; hazard ratio, 0.67; 95% CI, 0.43 to 1.03); among these patients, an unfavorable outcome on the Extended Glasgow Outcome Scale was reported in 43 of 78 patients (55%) and 49 of 72 (68%), respectively (relative risk, 0.81; 95% CI, 0.63 to 1.05). Adverse Events One patient in the conservative-oxygen group had hypoxemia with a Pao2 of 33.5 mm Hg, and a second patient had a low Spo2 but the actual value was not recorded; both of these episodes were reported as adverse events. One patient in the usual-oxygen group had an ischemic stroke that was reported as an adverse event.

DISCUSSION:

In this binational, multicenter, randomized clinical trial involving adults undergoing mechanical ventilation in the ICU, there was no significant difference in the number of ventilator-free days between those who received conservative oxygen therapy (as implemented in our trial) and those who received usual oxygen therapy. We did not find evidence of significant between-group differences in 90-day mortality, 180-day mortality, or survival. Our findings are at variance with the results of a previous single-center trial, which was stopped early after an unplanned interim analysis [19]. In that trial, conservative oxygen therapy in the ICU was associated with a greater number of ventilator-free days and a markedly lower rate of death than usual oxygen therapy [20]. In our trial, we prohibited the use of upper-limit Spo2 alarms in the usual-care group but did not take specific measures to target high Spo2 values. In the previous trial, a target Spo2 of 97 to 100% was used in the control group, and a Pao2 value of up to 150 mm Hg was allowed. In the usual-care group in our trial, the use of an Fio2 of less than 0.3 during invasive ventilation was discouraged, whereas in the previous trial, an Fio2 of more than 0.4 was suggested in the control group. Despite these differences, the observed exposure to oxygen as determined by the Pao2 level was similar in the usual-care group in our trial and in the control group in the previous trial. In addition to these differences in approach, the enrollment in our trial was much larger and thus provided more precise and robust estimates of treatment effects [21]. In our trial, there was a clear separation in oxygen exposure between the two groups. Patients in the conservative-oxygen group had a markedly lower number of hours with Spo2 of 97% or more and more hours breathing 0.21 oxygen than those in the usual-care group. Our data are suggestive of a possible benefit of conservative oxygen therapy in patients with suspected hypoxic–ischemic encephalopathy. It is biologically plausible that conservative oxygen therapy reduces the incidence of secondary brain damage after resuscitation from cardiac arrest, and observational data suggest that exposure to hyperoxemia in such patients may be harmful [22] [23] However, these findings should be considered hypothesis-generating. Our trial has several limitations. Clinicians and research staff members were necessarily aware of trial-group assignments. However, to mitigate ascertainment bias, centralized assessors conducted the evaluations at day 180 in a blinded manner. Some outcome variables (e.g., employment status) were compared only among survivors. Because survival was a post-randomization event, such data are not randomized comparisons and may be subject to bias. Some data, particularly related to quality of life and cognition, were missing. These data may not be missing at random because patients with better (or worse) outcomes might have been harder to contact or less likely to complete interviews. Despite these caveats, since problems with mobility and personal care are common after critical illnesses, our finding that relatively fewer survivors in the conservative-oxygen group had severe problems in these domains is potentially important [24] [25]. We compared the characteristics of trial patients with those of eligible patients who did not undergo randomization. Eligible patients who were not enrolled in the trial had less severe illness and lower rates of death than those who were enrolled. Accordingly, our findings may not apply to patients with less severe illness. Since we did not include mandates regarding weaning or extubation in the protocol, changes in the Fio2 , Spo2 , and Pao2 that occurred because of treatment assignment may have affected clinicians' decisions to wean and extubate particular patients. We allowed clinicians to increase oxygen in the two groups in some specific circumstances. This factor may have exposed patients in the two groups to hyperoxemia and thereby reduced our ability to detect a between-group difference in outcomes. In a recent systematic review and meta-analysis, investigators found that a conservative oxygen strategy was associated with a lower rate of death in acutely ill adults than a liberal oxygen strategy. In the trials that were included in this meta-analysis, many of the liberal oxygen interventions were considerably more liberal than the oxygen regimen used in our usual-care group, and relatively few of the patients were critically ill. Our trial does not preclude the possibility of benefit or

harm with more liberal oxygen regimens than those used in our usual-oxygen group. Different results may also be found with different regimens for conservative oxygen therapy. Our findings decrease the probability that the use of our protocol for conservative oxygen therapy in this population would result in markedly lower mortality than the use of usual oxygen therapy. However, the confidence intervals around our mortality estimates are sufficiently wide that we cannot rule out important effects of our conservative oxygen regimen on mortality.

In conclusion, during the first 28 days in the ICU, conservative oxygen therapy, as compared with usual oxygen therapy, did not significantly affect the number of ventilator-free days among adults undergoing mechanical ventilation.

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