Intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX): results of the pilot phase

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Although supplemental oxygen is delivered to all patients who require mechanical ventilation in the intensive care unit (ICU), the most appropriate "dose" of oxygen to use in such patients is uncertain.

In Australia and New Zealand, the standard approach to oxygen therapy in ICU patients who are mechanically ventilated appears to be relatively liberal.[1-3] It is biologically plausible that exposure to a high fraction of inspired oxygen (Fio_2)[4] or to abnormally high arterial oxygen partial pressure (Pao_2)[5-8] might be deleterious. The potential clinical consequences of liberal oxygen therapy are highlighted by observational studies suggesting that increasing hyperoxaemia is generally associated with increased mortality risk[9,10]and fewer ventilator-free days.[10]

Recent data from a single-centre randomised controlled trial have further heightened these concerns by suggesting that a liberal approach might increase mortality risk in ICU patients compared with a conservative oxygen therapy strategy.[11] However, this trial had a number of methodological problems, including that the primary analysis was not an intention to treat analysis; it was stopped early, without use of conventional stopping rules; there was a clinically important baseline imbalance between treatment groups; and the total number of mortality events was low.[12] In addition, its single-centre design and use of a protocolised standard care arm limit its external validity.

The relatively liberal approach to oxygen therapy that characterises current standard care[1-3] may, in fact, be preferred to a conservative approach of avoidance of hyperoxia because it provides a greater margin of safety against the development of hypoxaemia, which can lead to cellular hypoxia, organ dysfunction or even death.[13,14] The effect of a conservative approach to oxygen therapy on cognitive function has not been evaluated, although some data suggest that occurrence of hypoxaemia in

ABSTRACT

Objective: The objective of the intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX) pilot phase, which included the first 100 patients of an overall sample of 1000, was to examine feasibility.

Design: Investigator-initiated, prospective, parallel-group, pilot randomised controlled trial.

Setting: Six medical-surgical intensive care units (ICUs) in Australia and New Zealand, with participants recruited from September 2015 through June 2016.

Participants: 100 patients ≥ 18 years of age who required invasive mechanical ventilation in the ICU and were expected to be receiving it beyond the next calendar day at the time of randomisation.

Interventions: Conservative oxygen therapy or standard care.

Main outcome measures: Eligibility, recruitment rate, and separation in oxygen exposure (fraction of inspired oxygen [Fio_2] and oxygen saturation measured by pulse oximetry [Spo_2]).

Results: 94 of 99 participants (94.9%) were confirmed by study monitors to fulfil the study eligibility criteria. 3.6 patients per site per month were enrolled (95% confidence interval [CI], 2.5–4.7). Patients allocated to conservative oxygen therapy spent significantly more time on an Fio_2 of 0.21 in the ICU; median, 31.5 hours (interquartile range [IQR], 7–63.5) for conservative oxygen therapy patients *v* 0 hours for standard oxygen therapy patients (IQR, 0–10; midpoint difference, 21.5 hours; 95% CI, 9–34; $P < 0.0001$). Patients allocated to conservative oxygen therapy spent less time in the ICU with an Spo_2 of ≥ 97% than patients allocated to standard oxygen therapy; median, 18.5 hours (IQR, 5–46) for conservative oxygen therapy patients *v* 32 hours for standard oxygen therapy (IQR, 17–80; midpoint difference, 13.5 hours; 95% CI, 2–25; $P = 0.02$).

Conclusions: Our findings confirm the feasibility of completing the ICU-ROX trial without the need for substantive changes to the study protocol for the remaining 900 trial participants.

Trial registration: Australian and New Zealand Clinical Trials Registry (ANZCTRN 12615000957594).

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ICU is associated with an increased risk of adverse cognitive outcomes in ICU survivors.[15]

Accordingly, the relative merits of a conservative versus a standard care approach to oxygen therapy are unclear. To address the uncertainty, we are conducting a multicentre randomised clinical trial to evaluate the hypothesis that, compared with standard oxygen therapy, avoidance of hyperoxia (conservative oxygen therapy) will increase ventilator-free days[16] (ie, the number of days alive and free from requiring mechanical ventilation) in adult ICU patients who are mechanically ventilated and are expected to be ventilated beyond the day after tomorrow.

Here, we report the pilot phase of the intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX). This internal pilot phase included the first 100 patients of a planned overall sample of 1000. ICU-ROX has a considerably narrower enrolment window than previous trials evaluating oxygen therapy in ICU patients,[11,17] and differs in a number of other fundamental respects from previous trials, including that its control arm is a non-protocolised standard care arm. The rationale for conducting this phase was to establish that, despite these differences, our trial was feasible and would produce between group separation.

Methods

We conducted an investigator-initiated, prospective, parallel-group, pilot randomised controlled trial. The management committee designed the trial, which was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). The protocol was approved by the New Zealand Central Region Health and Disability Ethics Committee (15CEN14), the Austin Health Human Research Ethics Committee (HREC/15/Austin/23) and by each participating institution. Written informed consent before randomisation or consent to continue was obtained from each patient or legal surrogate, or an institutional ethics committee approved a waiver of consent. The study was prospectively registered on the Australian and New Zealand Clinical Trials Registry (ANZCTRN 12615000957594).

Patients

Patients aged ≥ 18 years who required invasive mechanical ventilation in the ICU and were expected to be receiving mechanical ventilation beyond the next calendar day at the time of randomisation were eligible for inclusion. The exclusion criteria are provided in Table 1. Enrolment was restricted to patients receiving less than 2 hours of invasive mechanical ventilation in an ICU. Patients who fulfilled all other eligibility criteria but were not enrolled within the 2-hour time window were categorised as "missed" rather than excluded for the purposes of describing participant flow.

We collected the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database[18] (ANZICS CORE APD) patient number for enrolled patients and for those who were eligible but were not enrolled (ie, patients who were "missed"). We sought to confirm in the pilot phase that it was feasible to use the ANZICS CORE APD to compare the characteristics of enrolled patients with eligible but missed patients with a view to doing this for the overall study.

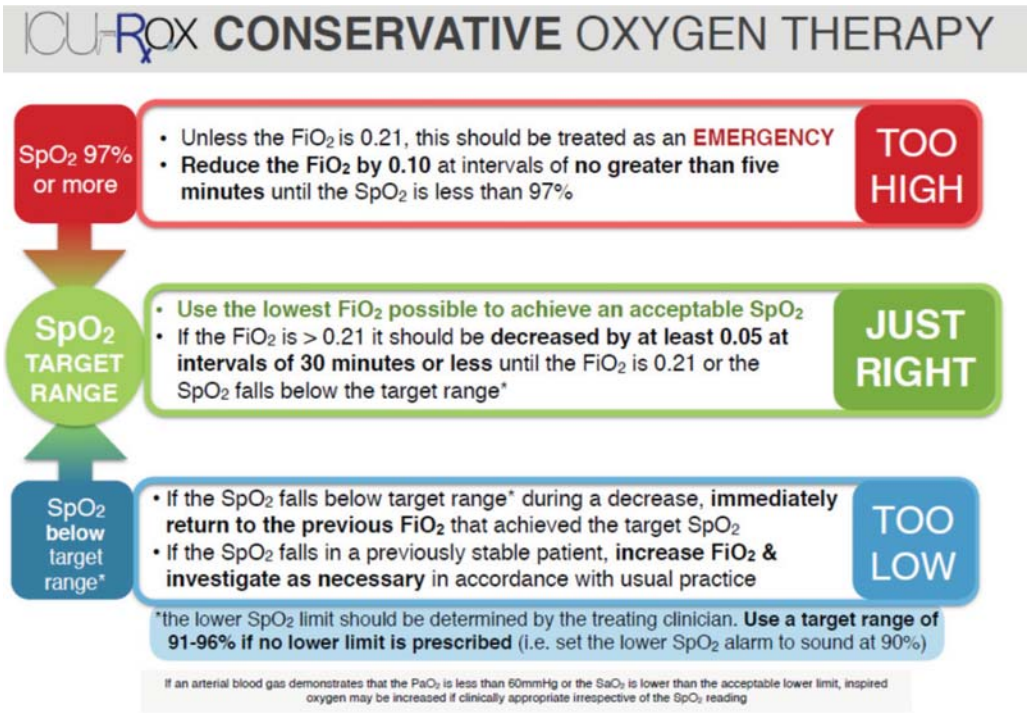
Study randomisation and treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive either conservative oxygen therapy (Figure 1) or standard care. An encrypted web-based system was used to assign patients to treatment arms using a variable block size with stratification by participating centre.

Table 1. Exclusion criteria

1. In the view of the treating clinician, hyperoxia is clinically indicated for reasons including (but not limited to) carbon monoxide poisoning or a requirement for hyperbaric oxygen therapy
2. In the view of the treating clinician, avoidance of hyperoxia is clinically indicated for reasons including (but not limited to) paraquat poisoning, previous exposure to bleomycin, or chronic hypercapnic respiratory failure
3. Pregnancy
4. Death is deemed to be inevitable as a result of the current acute illness and either the treating clinician, the patient, or the substitute decision maker are not committed to full active treatment
5. Patients with a life expectancy of less than 90 days due to a chronic or underlying medical condition
6. Admitted following a drug overdose (including alcohol intoxication)
7. Long-term dependence on invasive ventilation prior to this acute illness
8. Guillain-Barré syndrome, cervical cord injury above C5, muscular dystrophy, or motor neurone disease
9. Enrolment not considered in the patient's best interests
10. Previously enrolled in the ICU-ROX study
11. Greater than two hours of invasive mechanical ventilation and/ or non-invasive ventilation in an ICU during this hospital admission (includes time ventilated in another hospital's ICU)

Figure 1. Management of ventilated patients allocated to the conservative oxygen therapy arm*



Fio_2 = fraction of inspired oxygen. Spo_2 = oxygen saturation measured by pulse oximetry. * Conservative oxygen therapy intervention was applied from randomisation until intensive care unit (ICU) discharge, including after extubation. For patients assigned to conservative oxygen therapy, the inspired oxygen concentration was decreased to 0.21 or discontinued (in patients who had been extubated) as rapidly as possible, provided that the Spo_2 was greater than the lower limit acceptable to the treating clinician. Spo_2 levels > 96% were strictly avoided, and a monitored upper Spo_2 alarm limit of 97% was used whenever supplemental oxygen was being administered in the ICU.

In patients assigned to the conservative oxygen therapy group, the Fio_2 was decreased to 0.21 or discontinued (in patients who had been extubated) as rapidly as possible, provided that the arterial oxygen saturation by pulse oximetry (Spo_2) was greater than the lower limit acceptable to the treating clinician. Spo_2 levels > 96% were strictly avoided, and a monitored upper Spo_2 alarm limit of 97% was used whenever supplemental oxygen was being administered in the ICU. In the standard care arm, no specific measures were taken to avoid high Fio_2 or high Spo_2 and, in particular, the use of upper alarm limits for Spo_2 was prohibited.

In both treatment groups, monitored lower alarm limits for Spo_2 were set at 90%; however, a limit of lowest acceptable Spo_2 < 90% could be specified by the treating clinician if desired. In both treatment groups, if an arterial blood gas demonstrated that the Pao_2 was < 60 mmHg or the arterial oxygen saturation (Sao_2) was lower than the acceptable lower limit, Fio_2 was increased if clinically appropriate irrespective of the Spo_2 reading.

Patients continued study treatment until death, discharge from the study ICU, or Day 28 (672 hours) post-randomisation. The study intervention continued after extubation. If during the course of their ICU admission patients were transported outside of the ICU for radiological or other investigations or for procedures or operations, they received standard (non-study) treatment. Likewise, if an increase in Fio_2 was required for procedures performed in the ICU, including (but not limited to) bronchoscopy, suctioning, tracheostomy or preparation for extubation, this was permitted in both groups.

There were no restrictions to concomitant treatments provided to patients. In particular, the frequency of arterial blood gas analyses and the titration of positive end-expiratory pressure (PEEP) for patients in both arms of the trial were determined by the treating clinician.

Outcome measures and feasibility aims

The primary focus of this internal pilot study was to establish the feasibility of our study design. As well as evaluating specific outcome measures outlined below, we asked principal investigators and research coordinators to provide feedback on study protocols, study tools, the case report form, and data dictionary in order to refine these as required for the remaining study patients.

We aimed to confirm correct patient selection by demonstrating effective application of our eligibility criteria across multiple study centres. Study monitors from the Medical Research Institute of New Zealand (for New Zealand participants) and from the Australian and New Zealand Intensive Care Research Centre (for Australian participants) reviewed the participants' clinical records in order to verify that all participants fulfilled the eligibility criteria. We

aimed to demonstrate that our eligibility criteria could be effectively applied across multiple centres leading to at least 95% of enrolled patients fulfilling all eligibility criteria.

We aimed to show between treatment group separation and study protocol compliance. In particular, we aimed to show that the conservative oxygen therapy significantly reduced oxygen exposure, compared with standard care, without increasing exposure to hypoxaemia. In this regard, our hypotheses were that conservative oxygen would result in a statistically significantly increase in the mean proportion of hours when the Fio_2 was 0.21, would significantly decrease the mean proportion of hours when the Spo_2 was ≥ 97%, and would not significantly increase the proportion of hours when the Spo_2 was < 88%. The proportion of hours when the Fio_2 was 0.21 and the Spo_2 proportions described above were obtained from all values available on the ICU flow chart from randomisation until Day 28 (up to a maximum of one per hour). Additional metrics of oxygen exposure included mean, highest, and lowest daily Fio_2 and Pao_2. The mean values were obtained from 6-hourly recordings at 06:00, 12:00, 18:00, and 24:00 from randomisation (Day 0) until Day 10, while the highest and lowest values were obtained daily until Day 28 and included all available measurements (not just those used to calculate the mean value). For these metrics, Fio_2 was only recorded while patients were mechanically ventilated, but Pao_2 was recorded up until ICU discharge where it was available.

We aimed to show that the intervention would not result in a statistically significant difference in PEEP between treatment groups because we considered that differences in PEEP might be an important source of confounding. We recorded the mean, highest and lowest daily PEEP during invasive mechanical ventilation. The mean values were obtained from 6-hourly recordings at 06:00, 12:00, 18:00, and 24:00 from randomisation (Day 0) until Day 10, while the highest and lowest values were obtained daily until Day 28 and included all available measurements (not just those used to calculate the mean value).

Finally, we aimed to determine whether the recruitment rate achieved in the pilot phase would be sufficient to allow a 1000-participant trial to be completed in ten sites over a 36-month period (ie, that the recruitment rate would meet or exceed 2.8 patients per site per month).

We pre-specified that if some or all of the aims of the pilot were not achieved, then we would modify the protocol, or if necessary, we would abandon the study altogether in its current form.

For the main study, the primary outcome variable is alive-ventilator-free days to Day 28 (ventilator-free days). For the pilot phase we reviewed pooled outcome data (ie, not separated by treatment group) for ventilator-free days in order to confirm that estimates used for our sample size calculation were consistent with the observed overall standard deviation (SD) for this outcome variable. Study data related to patient-centred outcome variables including mortality, ICU-free days, and vasopressor-free days by treatment group were not revealed to the investigators for the pilot phase of the study. However, the data were reviewed by the Data Safety Monitoring Board as the first of two interim analyses planned for the study overall with appropriate alpha spending to preserve the overall alpha level of 0.05.

Statistical analysis

All data were initially assessed for normality. Baseline comparisons were performed using χ^2 tests for equal proportion (or Fisher exact tests where numbers were small), Student *t*-test for normally distributed data and Wilcoxon rank sum tests otherwise, with results reported as numbers (%), means ± SDs or medians (interquartile range [IQR]) respectively. Point estimates and 95% confidence intervals for non-parametric differences were calculated using the Hodges–Lehmann estimation. Comparison of longitudinal data was performed using mixed linear modelling, fitting main effects for treatment and time and an interaction between the two to determine if treatments differed over time. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, Unite States) and a two sided *P* value of 0.05 was used to indicate statistical significance.

Results

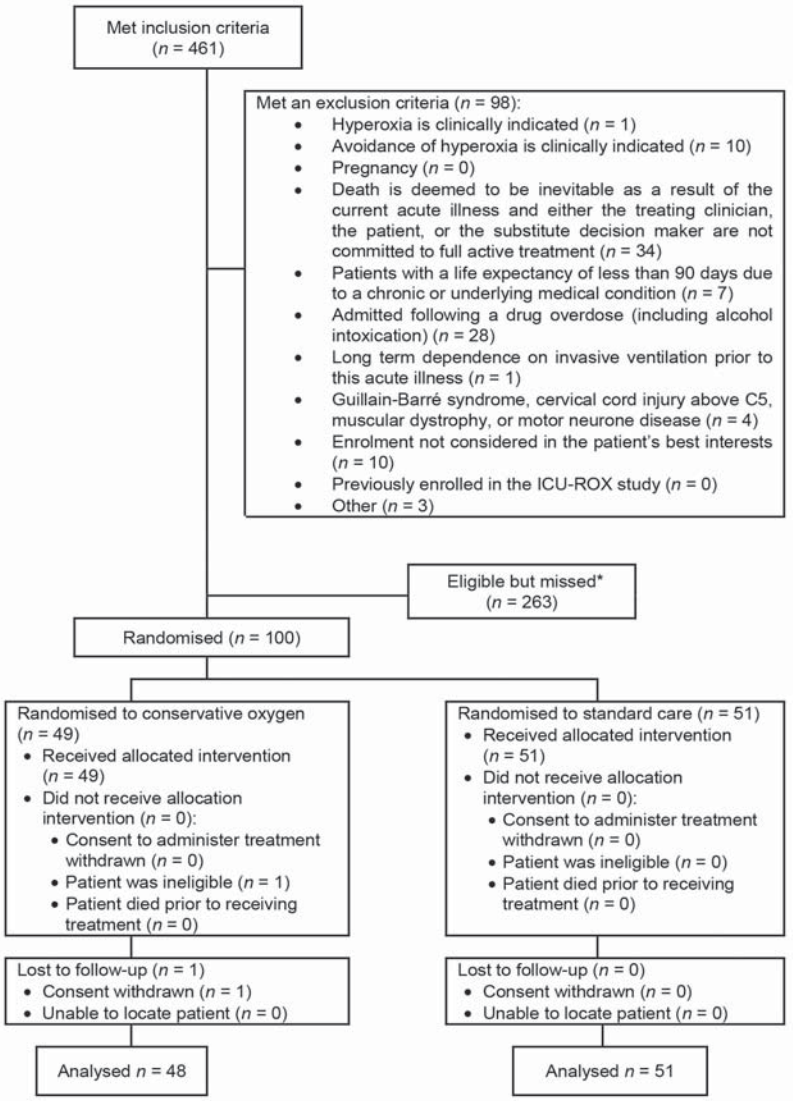
Patient characteristics

From September 2015 through June 2016, we enrolled 100 patients in six medical-surgical ICUs in Australia and New Zealand, with 49 patients assigned to receive conservative oxygen therapy and 51 assigned to standard care. One participant in the conservative oxygen therapy group withdrew consent, leaving an intention to treat population of 99 (Figure 2).

Patients were randomised a median of 1.5 hours (IQR, 0.8–2.8) after ICU admission; 1.7 hours (IQR, 0.8–2.4) and 1.4 hours (IQR, 0.9–3.4) for the conservative oxygen therapy group and the standard care group respectively ($P = 0.89$). The treatment groups had similar characteristics at baseline (Table 2). The most common admission diagnoses were cardiac arrest (21/99; 21%), bacterial pneumonia (8/99; 8%), septic shock (excluding urinary tract and patients coded as having pneumonia) (8/99; 8%), and soft tissue infections (5/99; 5%).

We were able to identify all "included patients" and all "eligible but missed" patients in the ANZICS CORE APD (Table 3). Included patients were older than missed patients (median age of 62 years [IQR, 52–71] and 57 years [IQR, 43–68] for included and missed patients respectively;

Figure 2. Flow of participants through the trial



* Patients categorised as "eligible but missed" fulfilled all eligibility criteria, but were not enrolled in the trial within the available 2-hour time window.

midpoint difference, 5.0 years; 95% CI, 2.0–9.0; $P = 0.01$), had higher illness acuity (median risk of death based on the Australian and New Zealand Risk of Death model, 23.3% [IQR, 8.2–47.3] and 17.4% [IQR, 3.7–44.2], for included and missed patients respectively; midpoint difference, 8%; 95% CI, 0.8–9.7; $P = 0.02$), and a higher in-hospital mortality rate (30 of 99 included patients [30.3%] and 52 of 263 missed patients [19.8%] died in hospital; $P = 0.03$).

Feasibility outcomes

Aim 1: To demonstrate effective application of eligibility criteria across multiple centres (correct patient selection)

Ninety-four of 99 participants (94.9%) were confirmed by study monitors reviewing clinical records to fulfil the study eligibility criteria. All five ineligible participants had received greater than 2 hours of invasive or non-invasive ventilation before enrolment. Of these, one had received 2 hours and 6 minutes of invasive ventilation, one had had a previous ICU ventilation episode during their hospital admission of more than 2 hours, and three were ineligible due to a period of more than 2 hours on non-invasive ventilation before randomisation.

Specific feedback provided by research coordinators and site investigators included that it was unclear whether or not patients with chronic obstructive pulmonary disease (COPD) should be excluded on the basis of exclusion criterion two (Table 1). Moreover, during study monitoring it was noted that one patient with a cervical cord injury above C5 had been included because, although this diagnosis had been suspected at the time of study enrolment, it was not confirmed at that time.

Aim 2: To demonstrate that conservative oxygen therapy reduced oxygen inspired and systemic exposure compared with standard care without increasing exposure to hypoxaemia (separation and compliance)

Patients allocated to conservative oxygen therapy spent significantly more time on an Fio_2 of 0.21 in the ICU (median 31.5 hours [IQR, 7–63.5] for patients in conservative oxygen therapy *v* 0 hours [IQR, 0–10] for patients in standard care; midpoint difference, 21.5 hours; 95% CI, 9–34; $P < 0.0001$) (Table 4). The mean Fio_2 while mechanically ventilated over the first 10 days in ICU, and the lowest Fio_2 and highest Fio_2 until Day 28 in ICU while ventilated by treatment group are shown in Figure 3; generally lower Fio_2 was used in the conservative oxygen therapy group. Patients allocated to conservative oxygen therapy spent less time in the ICU with an $Spo_2 \geq 97\%$ than patients allocated to standard oxygen therapy (median 18.5 hours [IQR, 5–46] for patients in conservative oxygen therapy *v* 32 hours [IQR, 17–80] for patients in standard care; midpoint difference, 13.5 hours; 95% CI, 2–25; $P = 0.02$). There were no differences between patients in conservative oxygen therapy and standard care with respect to the number or percentage of hours spent with an $Spo_2 < 91\%$ or with an $Spo_2 < 88\%$ (Table 4). The Pao_2 over the first 10 days in ICU, and the lowest Pao_2 and highest Pao_2 by treatment group are shown in Figure 4; generally, the Pao_2 was lower in the conservative oxygen therapy group.

Table 2. Characteristics of patients at baseline

Characteristic	Conservative oxygen therapy (*n* = 48)	Standard care (*n* = 51)	*P* value
Age (years)	61.4 ± 14.7*	59.7 ± 15.8*	0.59
Male sex	31 (64.6%)	35 (68.6%)	0.67
Comorbid conditions			
Cancer	1 (2.1%)	0 (0%)	0.49
Chronic pulmonary disease	0 (0%)	0 (0%)	1.00
Chronic cardiac disease	1 (2.1%)	0 (0%)	0.49
End stage renal failure	0 (0%)	1 (2%)	1.00
Immunosuppression by disease	0 (0%)	2 (3.9%)	0.5
Immunosuppression by therapy	3 (6.3%)	6 (11.8%)	0.34
Source of admission to ICU		0.96	
Emergency department	19 (39.6%)	21 (41.2%)	
Hospital ward	15 (31.3%)	13 (25.5%)	
Transfer from another ICU	2 (4.2%)	3 (5.9%)	
Transfer from another hospital (except from another ICU)	7 (14.6%)	9 (17.6%)	
From OT following elective surgery	5 (10.4%)	5 (9.8%)	
From OT following emergency surgery	19 (39.6%)	21 (41.2%)	
APACHE-II score†	22.8 ± 7.9*	21.4 ± 7.9*	0.38
Physiological support			
Inotrope/vasopressor support	30 (62.5%)	28 (54.9%)	0.44
Renal replacement therapy	1 (2.1%)	0 (0%)	0.49
Median (IQR) hours from ICU admission to randomisation	1.7 (0.8–2.4)	1.4 (0.9–3.4)	0.89

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range. OT = operating theatre. * Plus-minus values are means ± standard deviation. † Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

Table 3. Characteristics of enrolled patients v missed patients*

Characteristic	Enrolled patients (*n* = 99)	Missed patients (*n* = 263)	*P* value
Age (years), median (IQR)	62 (52–71)	57 (43–68)	0.01
Male (sex)	66 (66.7%)	169 (64.3%)	0.67
Illness severity (risk of death), median (IQR)			
ANZ ROD	23.3% (8.2–47.3)	17.4% (3.7–44.2)	0.017
ANZ ROD (no oxygen)†	23.4% (7.8–48.1)	16.6% (3.52–40.6)	0.018
APACHE-III ROD	34.5% (15.6–68.0)	23.4% (7.82–48.1)	0.004
Major APACHE-III diagnostic groups			
Cardiovascular	36 (36.4%)	58 (22.1%)	0.006
Gastrointestinal	6 (6.1%)	25 (9.5%)	0.3
Musculoskeletal	7 (7.1%)	9 (3.4%)	0.13
Neurological	8 (8.1%)	45 (17.1%)	0.03
Respiratory	24 (24.2%)	54 (20.5%)	0.44
Sepsis	10 (10%)	21 (8%)	0.52
Trauma	7 (7.1%)	43 (16.3%)	0.02
Other	1 (1%)	8 (3%)	0.27
Source of admission to ICU			0.96
Emergency department	40 (40.4%)	94 (35.7%)	0.41
Hospital ward	26 (26.3%)	29 (11.0%)	< 0.001
Transfer from another hospital	7 (7.1%)	66 (25.1%)	< 0.001
Operating theatre	26 (26.3%)	74 (28.1%)	0.72
Length of stay (days), median (IQR)			
ICU length of stay	4.6 (2.2–8.1)	5.16 (2.7–10.2)	0.45
Hospital length of stay	13.9 (6.4–26.8)	14.3 (7.3–29.0)	0.46
In-hospital mortality	30 (30.3%)	52 (19.8%)	0.03

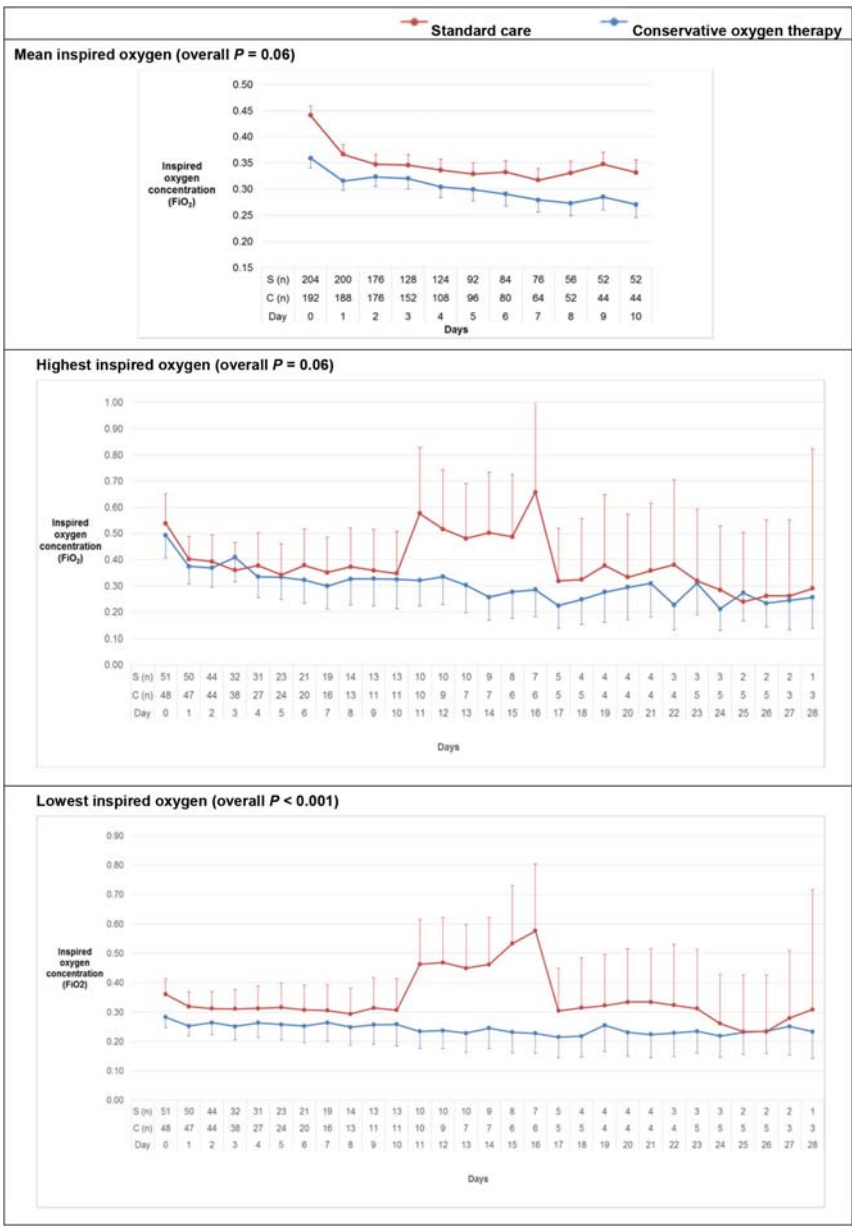
APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range. OT = operating theatre. * Plus-minus values are means ± standard deviation. † Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

Table 4. Separation in oxygen exposure*

Characteristic	Conservative oxygen therapy (*n* = 48)	Standard care (*n* = 51)	*P* value
Hours $Spo_2 \geq 97\%$			
mean % of hours per patient$Spo_2 \geq 97\%$	27%	45%	0.002
median (IQR) proportion of hours per patient $Spo_2 \geq 97\%$	0.20 (0.07–0.34)	0.41 (0.15–0.79)	0.003
median (IQR) number of hours per patient $Spo_2 \geq 97\%$	18.5 (5–46)	32 (17–80)	0.02
Hours $Spo_2 < 91\%$			
mean % of hours per patient $Spo_2 < 91\%$	6%	5%	0.26
median (IQR) proportion of hours per patient $Spo_2 < 91\%$	0.02 (0–0.06)	0.01 (0–0.04)	0.26
median (IQR) number of hours per patient $Spo_2 < 91\%$	2.5 (0–11)	1 (0–5)	0.18
Hours $Spo_2 < 88\%$			
mean % of hours per patient$Spo_2 < 88\%$	2%	2%	0.20
median (IQR) proportion of hours per patient $Spo_2 < 88\%$	0 (0–0.01)	0 (0–0.01)	0.20
median (IQR) number of hours per patient $Spo_2 < 88\%$	0 (0–2)	0 (0–1)	0.20
Hours Fio_2 0.21			
mean % of hours per patient with an Fio_2 of 0.21	38%	10%	< 0.001
median (IQR) proportion of hours per patient with an Fio_2 of 0.21	0.29 (0.06–0.64)	0 (0–0.13)	< 0.001
median (IQR) number of hours per patient with an Fio_2 of 0.21	31.5 (7.0–63.5)	0 (0–10)	< 0.001

Fio_2 = fraction of inspired oxygen. IQR = interquartile range. Spo_2 = oxygen saturation measured by pulse oximetry * Spo_2 hours above and below specified thresholds and hours on an Fio_2 of 0.21 were obtained from all values recorded on the intensive care unit flow chart (up to a maximum of one value per hour) up until Day 28 post-randomisation, including after extubation even where supplemental oxygen therapy was not being administered.

Figure 3. Daily mean, highest and lowest fraction of inspired oxygen (Fio_2) by treatment group



C = conservative oxygen therapy. Fio_2 = fraction of inspired oxygen. S = standard care. Error bars are standard error means. The number of observations on each day is indicated on the horizontal axis. For the mean Fio_2, a maximum of four values per patient per day (recorded 6-hourly) were available; for highest and lowest Fio_2, a maximum of one value per patient per day was available.

Aim 3: To demonstrate that conservative oxygen therapy did not result in a difference in PEEP between treatment groups (confounder minimisation)

Patients allocated to conservative oxygen therapy were treated with similar levels of PEEP to patients allocated to standard care (Figure 5).

Aim 4: To demonstrate a recruitment rate of at least 2.8 patients per site per month (recruitment rate feasibility)

The observed recruitment rate over the internal pilot phase was 3.6 patients per site per month (95% CI, 2.5–4.7).

Pooled outcome data for ventilator-free days

The mean ± SD ventilator-free days were 16 ± 12 days (median 23 days; IQR, 0–27). This compares to baseline ventilator-free days used in our sample size calculation of 16.4 ± 11.3 days.

Adverse events (safety)

In one patient allocated to the conservative oxygen therapy arm, an adverse event was reported for inadvertent exposure to hypoxaemia. In this patient, the Fio_2 was reduced from 0.40 to 0.30 and then further reduced to 0.21, in accordance with the protocol, because the Spo_2 was reading 98%. An arterial blood gas was then performed and showed a Sao_2 of 62.3% and a Pao_2 of 33.5 mmHg, despite the pulse oximeter still reading 98%. The Fio_2 was increased immediately following this. No specific cause for the apparent pulse oximeter inaccuracy was identified. This patient died a number of days after this event from progressive respiratory failure; the death was not considered related to the adverse event.

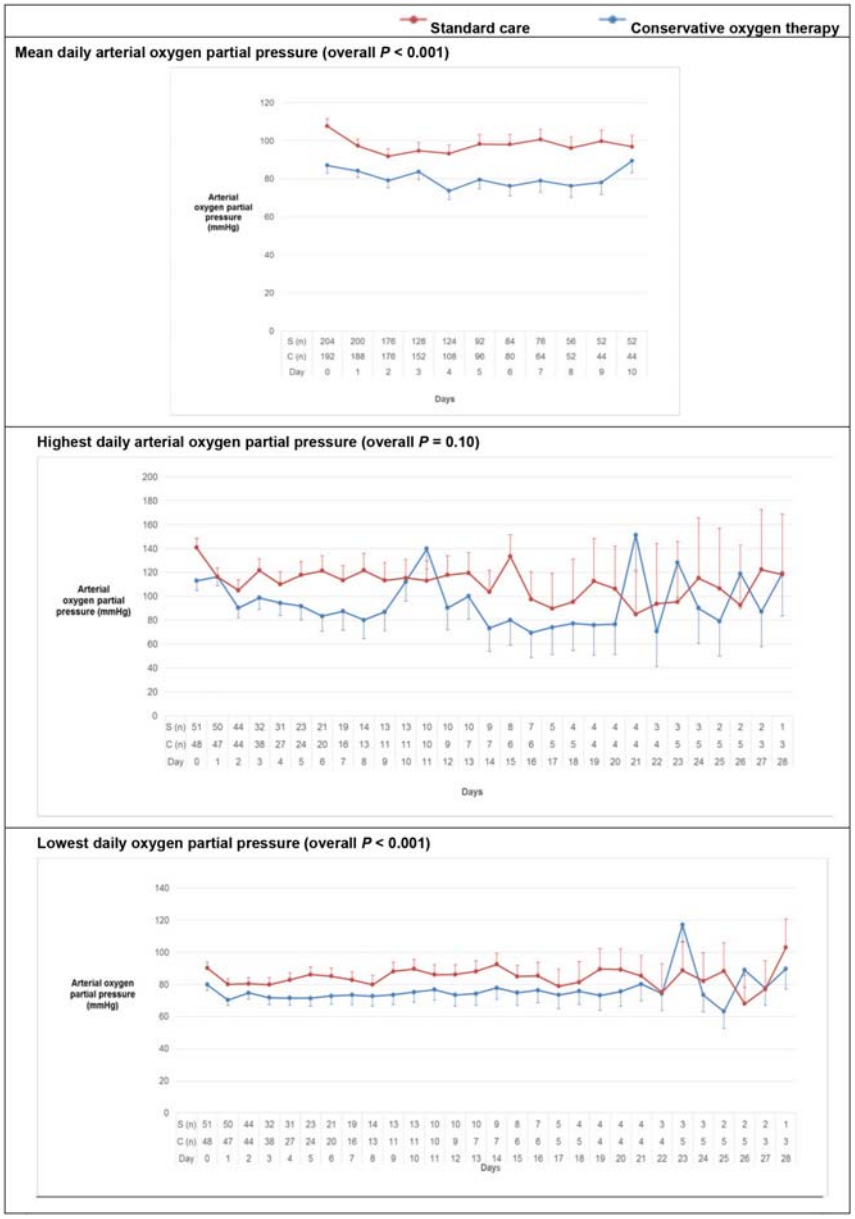
Interim analysis

Data were reviewed by the Data Safety Monitoring Board who recommended that the study continue.

Discussion

We conducted a multicentre feasibility study with a sample comprising the first 100 participants of a planned 1000-participant randomised clinical trial comparing conservative oxygen therapy to standard care. Our eligibility criteria were successfully applied with 95% of participants confirmed to fulfil the eligibility criteria. We demonstrated

Figure 4. Mean, highest and lowest arterial partial pressure of oxygen (Pao_2) by treatment group



C = conservative oxygen therapy. S = standard care. Error bars are standard error means. The number of observations on each day is indicated on the horizontal axis. For the mean Pao_2 a maximum of four values per patient per day (recorded 6-hourly) were available; for highest and lowest Pao_2, a maximum of one value per patient per day was available.

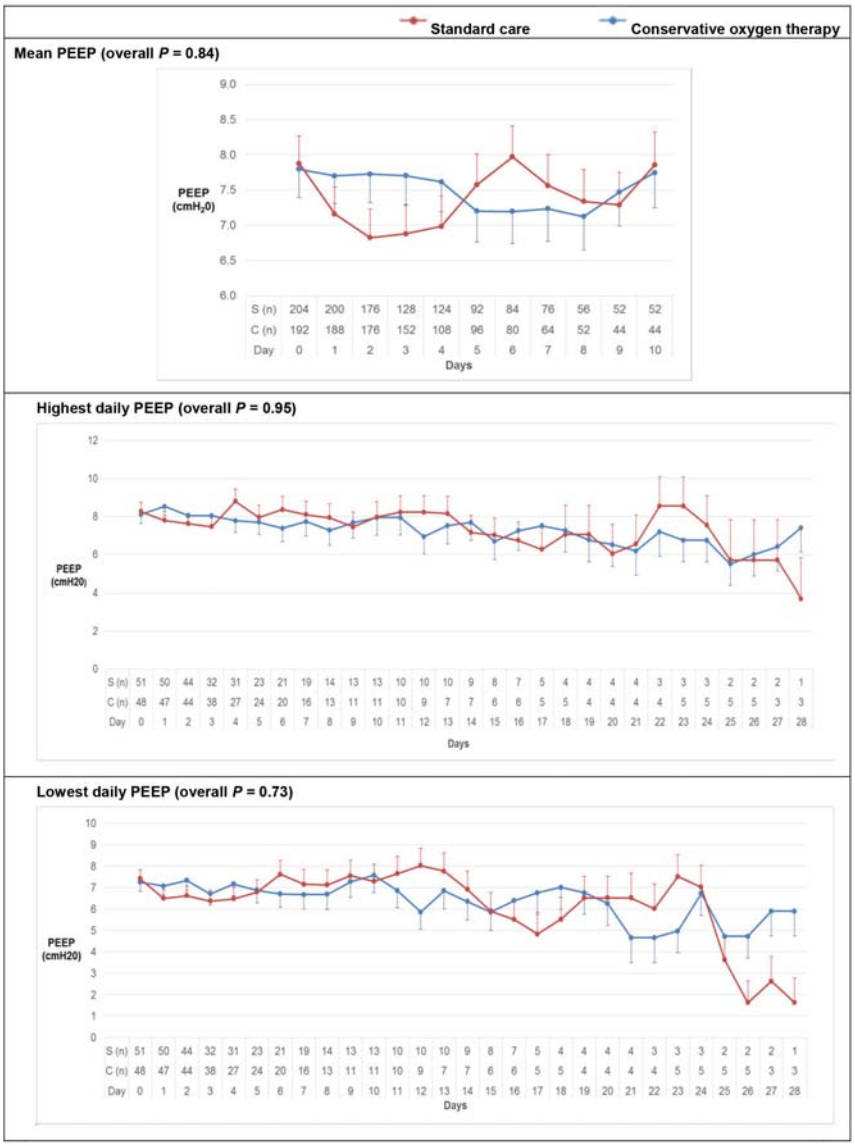
between treatment group separation and compliance, showing that conservative oxygen therapy significantly reduced oxygen exposure to an Fio_2 above 0.21, and reduced Spo_2 and Pao_2 without significantly increasing Spo_2 below 88%. This treatment separation was achieved without a significant effect on the PEEP level delivered.

Patients in the ICU-ROX pilot were randomised a median of 1.5 hours (IQR, 0.8–2.8) after ICU admission; we excluded patients who were ventilated in ICU for more than 2 hours. Because exposure to hyperoxaemia typically occurs in the early stages following ICU admission,[3] rapid enrolment of trial participants is an important point of difference in the ICU-ROX pilot compared with previous randomised controlled trials of oxygen therapy in ICU.[11,17] The mean ± SD duration of mechanical ventilation before randomisation in the CLOSE trial was 13 ± 7 hours.[17] The Oxygen-ICU study did not report the time from ICU admission to randomisation;[11] however, as there was no time window within which enrolment needed to occur, it is likely that many patients in this trial were enrolled some time after ICU admission.

Our 2-hour enrolment window may have made enrolment logistically challenging in some cases. This is one potential explanation for why 263 of 363 participants (74.4%) were categorised as eligible for enrolment but missed. In the ICU-ROX pilot, for the first time in an ANZICS CTG trial, we compared the characteristics of eligible enrolled patients with eligible missed patients using data from ANZICS CORE APD. This comparison indicated that there were statistically significant differences, possibly indicating selection bias with enrolled patients having higher illness acuity and higher in-hospital mortality rates than missed patients. Despite this, our study population, like the CLOSE study population,[17] included a broad cohort of ICU patients. Around 90% of patients included in our study were "emergency admissions" and all were invasively mechanically ventilated. This is in contrast to the Oxygen-ICU trial,[11] where a third of the patients enrolled were not invasively ventilated at baseline.

Both the CLOSE trial[17] and the Oxygen-ICU trial[11] had protocolised treatment in the liberal arm. To avoid the problem of practice misalignment,[19] where neither arm of a study resembles standard practice, we chose not to protocolise treatment in the liberal (standard care) arm of the ICU-ROX trial. Despite this, we achieved significant reductions in both Fio_2, limiting potential pulmonary toxicity from oxygen, and in Pao_2, limiting potential systemic oxygen

Figure 5. Mean, highest and lowest positive end-expiratory pressure (PEEP) by treatment group



C = conservative oxygen therapy. S = standard care. Error bars are standard error means. The number of observations on each day is indicated on the horizontal axis. For the mean PEEP, a maximum of four values per patient per day (recorded 6-hourly) were available; for highest and lowest PEEP, a maximum of one value per patient per day was available.

toxicity using conservative oxygen therapy.

While our results support the overall feasibility of the study, based on our experience conducting the pilot phase, we have made a number of minor refinements to the ICU-ROX protocol for the remaining 900 participants. The use of an Fio_2 of 0.21 while mechanically ventilated in the standard care arm was higher than anticipated.[3] Therefore, we have added the following guidance to the protocol for patients allocated to the standard care arm: "The use of an Fio_2 of less than 0.3 while ventilated is discouraged". We have done this to minimise the risk of contamination occurring for the remaining trial participants, while remaining consistent with current standard practice. In addition, regular reports will be sent to sites to highlight any instances when an Fio_2 of less than 0.3 is administered to patients who are mechanically ventilated in the standard care arm. The observation that PEEP levels did not differ by treatment group supports our plan not to protocolise PEEP in the ICU-ROX trial.

Exclusion criterion two will be modified to specifically exclude patients with COPD. This is in response to uncertainty from sites about the eligibility of such participants, and to reflect the fact that conservative oxygen therapy is typically recommended in such patients.[20] The new criterion will read as follows: "In the view of the treating clinician, avoidance of hyperoxia is clinically indicated for reasons including (but not limited to) chronic obstructive pulmonary disease (COPD), paraquat poisoning, previous exposure to bleomycin, or chronic hypercapnic respiratory failure". Following the inclusion of a patient with a suspected cervical cord injury above C5, exclusion criterion eight will be modified to include patients with suspected cervical cord injury above C5 as well as those with a confirmed diagnosis. The new criterion will read as follows: "Suspected or confirmed diagnosis of any of the following: Guillain-Barré syndrome, cervical cord injury above C5, muscular dystrophy, or motor neurone disease".

In addition, a specific exclusion criterion of "enrolled in any other trial of targeted oxygen therapy" has been added, because a randomised trial evaluating conservative oxygen therapy in the pre-hospital setting in post-cardiac arrest patients, the Reduction of Oxygen after Cardiac Arrest (EXACT) trial, will shortly commence recruitment in Australia.

In response to the single adverse event, and with the support of the Data Safety Monitoring Board, we have modified the wording of the intervention in the study protocol to include the following statement: "The treating clinician is encouraged to follow their usual practice with respect to performing arterial blood gases when adjustments

to Fio_2 are made. However, when the Fio_2 has been stable for a prolonged period, clinicians are encouraged to perform a blood gas when substantial adjustments to Fio_2 are being made".

Finally, the observed SD of ventilator-free days of 12 days is similar to the SD of 11.3 days used in our sample size calculation for the overall study and so, no change to the sample size of 1000 participants has been made following the pilot phase.

Conclusion

In the ICU-ROX pilot phase we showed a significant reduction in inspired oxygen exposure, Spo_2, and Pao_2 using conservative oxygen therapy compared with standard care. These reductions were achieved without a concomitant increase in time spent with low pulse oximetry saturations. These findings confirm the feasibility of completing the ICU-ROX trial without the need for substantive changes to the study protocol for the remaining 900 trial participants.

Competing interests

None declared.

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