Associations between the intraoperative fraction of inspired intraoperative oxygen administration and days alive and out of hospital after surgery

Daniel R. Frei[1,2,*,†], Matthew R. Moore[3,†], Michael Bailey[4], Richard Beasley[2,5], Douglas Campbell[3,6], Kate Leslie[7,8,9], Paul S. Myles[9,10], Timothy G. Short[2,6] and Paul J. Young[2,4,8,11]

[1]Department of Anaesthesia and Pain Management, Wellington Hospital, Wellington, New Zealand, [2]Medical Research Institute of New Zealand, Wellington, New Zealand, [3]Department of Anaesthesiology, University of Auckland, Auckland, New Zealand, [4]Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, [5]Victoria University of Wellington, Wellington, New Zealand, [6]Department of Anaesthesia and Peri-operative Medicine, Auckland City Hospital, Auckland, New Zealand, [7]Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Victoria, Australia, [8]Department of Critical Care, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia, [9]Department of Anaesthesiology and Perioperative Medicine, Central Clinical School, Faculty of Medicine, Nursing, and Health Sciences, Monash University, Melbourne, Victoria, Australia, [10]Department of Anaesthesiology and Perioperative Medicine, Alfred Hospital Melbourne, Victoria, Australia and [11]Department of Intensive Care, Wellington Regional Hospital, Wellington, New Zealand

*Corresponding author. Department of Anaesthesia and Pain Management, Wellington Hospital, 49 Riddiford Street, Newtown, Wellington 6021, New Zealand.
 E-mail: daniel.frei@ccdhb.org.nz
 Twitter: @DanielRetoFrei ; @matt_r_moore ; @katy_skier ; @DogICUma
[†]Contributed equally to this work.

Abstract

Background: There is limited knowledge about the effect of liberal intraoperative oxygen on non-infectious complications and overall recovery from surgery.

Methods: In this retrospective cohort study, we investigated associations between mean intraoperative fraction of inspired oxygen (FiO_2), and outcome in adults undergoing elective surgery lasting more than 2 h at a large metropolitan New Zealand hospital from 2012 to 2020. Patients were divided into low, medium, and high oxygen groups ($FiO_2 \leq 0.4$, 0.41−0.59, ≥ 0.6). The primary outcome was days alive and out of hospital at 90 days ($DAOH_{90}$). The secondary outcomes were post-operative complications and admission to the ICU.

Results: We identified 15,449 patients who met the inclusion criteria. There was no association between FiO_2 and $DAOH_{90}$ when high FiO_2 was analysed according to three groups. Using high FiO_2 as the reference group there was an adjusted mean (95% confidence interval [CI]) difference of 0.09 (−0.06 to 0.25) days (P = 0.25) and 0.28 (−0.05 to 0.62) days (P = 0.2) in the intermediate and low oxygen groups, respectively. Low FiO_2 was associated with increased surgical site infection: the adjusted odds ratio (OR) for low compared with high FiO_2 was 1.53 (95% CI 1.12−2.10). Increasing FiO_2 was associated with respiratory complications: the adjusted OR associated with each 10% point increase in FiO_2 was 1.17 (95% CI 1.08−1.26) and the incidence of being admitted to an ICU had an adjusted OR of 1.1 (95% CI 1.03−1.18).

Conclusions: We found potential benefits, and risks, associated with liberal intraoperative oxygen administration indicating that randomised controlled trials are warranted.

The fraction of inspired oxygen (FiO$_2$) administered to patients receiving general anaesthesia is mostly greater than 0.21, which is the FiO$_2$ in room air. There are many reasons why the anaesthetist may administer oxygen to maintain a percentage saturation of arterial haemoglobin with oxygen (SaO$_2$) as measured by a pulse oximeter (SpO$_2$) at a supra-physiological saturations. In anaesthesia practice, supra-physiological oxygen administration avoids low oxygen concentrations in arterial blood (hypoxaemia) that could cause tissue injury and may optimise oxygen delivery to vulnerable tissues. Relatedly, a high FiO$_2$ may be used to increase the oxygen store in the lungs to prolong the apnoeic desaturation time during induction of or emergence from anaesthesia, with the aim of reducing the likelihood of clinically significant hypoxaemia during airway manipulation.[1] In addition, some perioperative guidelines advocate for the administration of high FiO$_2$ during and after surgery in the hope that it might reduce the risk of post-operative surgical site infection.[2]

By contrast, it is biologically plausible that liberal oxygen is harmful. For example, an increase in oxygen-induced reactive oxygen species generated as a result of high FiO$_2$ may overwhelm the reductive capacity of tissues, resulting in cellular dysfunction and death.[3,4] Studies in related specialties of acute medicine[5,6] and intensive care[7,8] have reported increased morbidity and mortality with routine liberal oxygen therapy, and recent retrospective perioperative studies have suggested an association between FiO$_2$ and post-operative pulmonary complications, as well as acute kidney and myocardial injury.[9,10] However, there is a lack of evidence relating to the effect of high FiO$_2$ on overall recovery from surgery.

We, therefore, undertook a retrospective cohort study aiming to investigate the strength and nature of associations between intraoperative FiO$_2$ and overall recovery from surgery and a range of post-operative complications in adult patients undergoing elective surgery. We hypothesised that high intraoperative FiO$_2$ would be associated with fewer days alive and out of hospital at 90 days (DAOH₉₀; an overall measure of recovery), and an increased incidence of post-operative complications.

Methods

Ethical approval was obtained from the New Zealand Central Health and Disability Ethics Committee (21/CEN/141), and locality approval from the Auckland District Health Board Research Review Committee. The study has been reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11]

Eligible patients were adults (≥18-yr old on the operation date) undergoing elective surgery, with ASA physical status (PS) 1–4 and with an operative duration of between 120 and 720 min at Auckland City Hospital between July 2, 2012, and June 30, 2020. We chose July 2, 2012, as the start of the recruitment period because after this date the specification of the New Zealand Ministry of Health National Minimum Dataset (NMDS) was updated to include a 'condition onset flag' for diagnosis codes. The 'condition onset flag' indicates when a diagnosis or complication has arisen during a given hospital admission event. This flag enables the identification of new complications during admission, and, therefore, the differentiation of these from baseline comorbidities. Operations lasting longer than 720 min were excluded because a high proportion of these cases were expected to be artifactual as a result of the anaesthesia record not being ended at the completion of anaesthesia care. Patients undergoing cardiac, thoracic, and obstetric surgery were excluded. Eligible patients were identified from hospital records. If a patient underwent more than one surgical procedure during an admission of interest, only the first procedure was considered. Procedures were further excluded if they could not be matched from hospital records to the Anaesthetic Information Management System (AIMS) or national records, or if those records were missing or contained erroneous key variables. There was no imputation of missing data. If a patient had more than one eligible admission event involving a planned surgical procedure over the study period, one was selected at random to avoid inflation of outcomes earlier in the study period.

Data were derived from the Auckland City Hospital electronic medical record, the SAFERsleep (SAFERSleep, Safer Sleep LLC, Delaware, USA and Auckland, New Zealand) AIMS, and the NMDS. Baseline and outcome variables were obtained from the NMDS,[12] which codes clinical data using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM), the Australian Classification of Health Interventions (ACHI), and Australian Coding Standards (ACS).[12] Exposure variables were obtained from the SAFERsleep AIMS. FiO$_2$ and SpO$_2$ values were sampled at either 10-, 30-, or 60-s intervals as determined by the configuration of individual SAFERsleep AIMS, and mean values were calculated accordingly for each study participant. Hospital records were matched to the anaesthetic database on the operation identifier, and to national records on the admission identifier. Participants were identified by an encrypted version of their unique National Health Index number; data were obtained and combined to provide the study variable set.

The primary outcome was DAOH₉₀ (hospitals in this case included any acute, subacute, or planned care hospital and aged care, respite, or hospice facility in New Zealand). The count included the day of surgery, and any of the subsequent 90 days that were spent (partially or wholly) in 'hospital' or dead were subtracted from the total.[13] The secondary outcomes were post-operative surgical site infection, respiratory complications, non-infection-related complications, death within 90 days of surgery, and post-operative ICU admission. Specifically, respiratory complications included all ICD-10-AM codes that related to pulmonary infectious complications and pulmonary non-infectious complications. Non-infection-related complications included all ICD-10-AM codes relating to transient ischaemic attack, cerebrovascular accident, myocardial infarction, and pulmonary embolism. ICU admission included all patients admitted to the combined ICU and high dependency unit (HDU) at Auckland City Hospital. The sampling period covered 8 yr (96 months). It was estimated that this would include 15,000 patients after the removal of

duplicates. We calculated that with approximately 5000 patients in each of the three groups defined by mean intraoperative FiO_2 exposure (low FiO_2, ≤ 0.40; intermediate FiO_2, 0.41–0.59; high FiO_2, ≥ 0.60), this study would have a 90% power at $\alpha = 0.0167$ (0.05/3) to detect a difference in proportions between any two groups equal to 4% and a difference in continuous variables equal to 7.5% of 1 standard deviation.

Statistical analyses

The primary outcome ($DAOH_{90}$) and all continuous secondary outcomes were analysed using median regression with results reported as point estimates (95% confidence interval [CI]). The secondary binomial outcomes were analysed using logistic regression and reported as odds ratios (ORs; 95% CI). To explore the relationship between outcome and exposure, FiO_2 was initially analysed as a categorical variable, considering three categories of mean intraoperative FiO_2 (low FiO_2, ≤ 0.40; intermediate FiO_2, 0.41–0.59; and high FiO_2, ≥ 0.60). These oxygen bands were chosen to achieve sufficient numbers across groups to enable meaningful statistical comparisons while maintaining three distinct concentrations of oxygen administration. Where there was evidence of a linear relationship, FiO_2 was further analysed as a continuous variable and presented as the change in incidence associated with a 10% point increase in FiO_2.

All analyses were adjusted for *a priori* determined covariates known to impact outcome including age, sex, ASA-PS, smoking status, BMI, Charlson Comorbidity Index (CCI), intraoperative PEEP, surgery type, duration of surgery, year of admission, and day and time of surgery. To provide data on Māori health inequity, we conducted pre-specified subgroup analysis according to the baseline criteria of Māori *vs* European ethnicity as a baseline comparator. Other pre-specified subgroup analyses were cancer *vs* non-cancer surgery, diabetes *vs* non-diabetes, ASA-PS 1 or 2 *vs* 3 or 4 (ASA-PS 3 and 4 were pooled due to the anticipated low number of ASA-PS 4 patients), with heterogeneity determined by fitting interactions between FiO_2 and subgroup. Statistical analyses were performed using R version 4.2 (R Foundation, Vienna, Austria) and SAS version 14.3 (SAS Institute, Cary, NC). All tests of significance were two-tailed, and P-values <0.05 for the primary outcome and <0.01 for the secondary outcomes were considered to indicate statistical significance.

Results

Hospital records contained 30,035 eligible operations, of which 15,449 met the study inclusion criteria (see Fig 1) and were included in the study analyses. Among the participants, 51.8% ($n = 8007$) were female and 48.2% ($n = 7442$) were male, with a mean age of 56 (SD 16) yr, and median (inter-quartile range [IQR]) ASA-PS of 2 (2–3). The commonly reported ethnic groups of patients were Asian ($n = 1992$, 12.9%), European ($n = 9297$, 60.2%), Māori ($n=1845$, 11.9%), and Pacific Peoples ($n = 1939$, 12.6%). The baseline characteristics of the participants are presented in Table 1.

The time-weighted mean intraoperative FiO_2 for all study participants was 0.55 (0.09). When participants were divided into three categories of oxygen exposure, 617 participants had a mean FiO_2 of 0.36 (0.04) in the low-oxygen group, 10,867 participants had an average FiO_2 of 0.52 (0.05) in the intermediate-oxygen group, and 3965 participants had an average intraoperative FiO_2 of 0.66 (0.06) in the high-oxygen group. The mean SpO_2 was 97.8% (1.3%) in the low oxygen
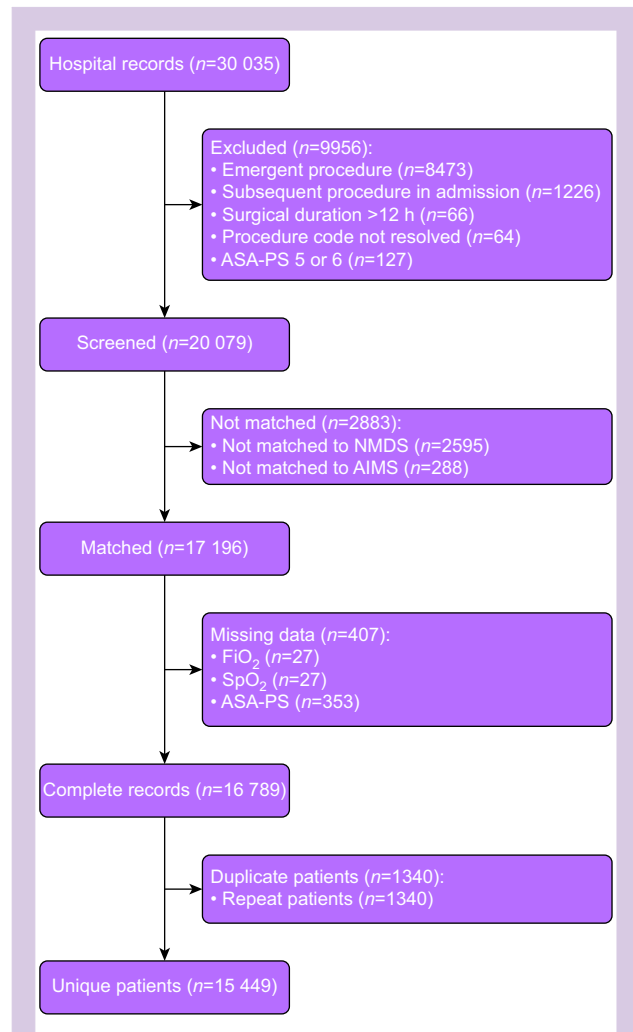

Fig 1. Patient flow diagram illustrating inclusion in the study. AIMS, Anaesthetic Information Management System; FiO_2, fraction of inspired oxygen; NMDS, National Minimum Dataset; PS, physical status; SpO_2, percentage haemoglobin saturation with oxygen as measured by a pulse oximeter.

category, 98.1% (1.1%) in the intermediate category, and 98% (1.3%) in the high oxygen category, ($P < 0.001$). The minimum SpO_2 was 87.3% (1.1%), 88.9% (1.0%), and 88.1% (1.1%), respectively, for low, intermediate, and high FiO_2 categories ($P < 0.001$). The administered FiO_2 displayed a significant annual decline throughout our study at a rate of between 0.0097 and 0.0103 ($P < 0.0001$) per year (see Fig 2).

$DAOH_{90}$

$DAOH_{90}$ differed according to the FiO_2 category with a lower $DAOH_{90}$ in the low oxygen category (median [IQR] low 83 [78–85], intermediate 84 [79–86], and high 84 [80–86]; $P = 0.03$). However, after multivariable adjustment for baseline imbalance, this relationship was no longer significant when comparing the three FiO_2 categories: using the high FiO_2 group as the reference, the median (95% CI) difference in $DAOH_{90}$ was 0.09 (−0.06 to 0.25) for intermediate and 0.28 (−0.05 to 0.62) for low oxygen categories. When treating FiO_2 as a continuous

Table 1 Patient baseline characteristics. CCI, Charlson Comorbidity Index; IQR, inter-quartile range; PS, physical status.

Characteristics	Low	Intermediate	High	P-value
N	617	10,867	3965	
Age, mean (SD)	52.1 (17.1)	55.8 (16.5)	56.7 (16.3)	<0.0001
Sex, n (%)				
Female	278 (45.1)	5620 (51.7)	2111 (53.2)	0.0007
Male	339 (54.9)	5247 (48.3)	1854 (46.8)	0.0007
Ethnicity, n (%)				
Asian	93 (15.1)	1413 (13)	486 (12.3)	0.13
European	375 (60.8)	6582 (60.6)	2340 (59)	0.22
Māori	73 (11.8)	1278 (11.8)	494 (12.5)	0.51
Middle Eastern	16 (2.6)	192 (1.8)	70 (1.8)	0.32
Pacific Peoples	54 (8.8)	1333 (12.3)	552 (13.9)	0.0004
Other	3 (0.5)	16 (0.1)	6 (0.2)	0.12
Unknown	3 (0.5)	53 (0.5)	17 (0.4)	0.9
BMI (kg/m^2), n (%)				
<18.5	7 (1.1)	69 (0.6)	27 (0.7)	0.33
18.5 to <25	111 (18)	1402 (12.9)	381 (9.6)	<0.0001
25 to <30	100 (16.2)	1508 (13.9)	428 (10.8)	<0.0001
30 to <35	81 (13.2)	1516 (14)	603 (15.2)	0.11
35 to <40	11 (1.8)	340 (3.1)	190 (4.8)	<0.0001
≥40	7 (1.1)	80 (0.7)	57 (1.4)	0.0004
Unknown	300 (48.6)	5952 (54.8)	2279 (57.5)	0.0001
ASA-PS, n (%)				
1	92 (14.9)	1559 (14.3)	453 (11.4)	<0.0001
2	305 (49.4)	5364 (49.4)	1815 (45.8)	0.0005
3	207 (33.5)	3716 (34.2)	1582 (39.9)	<0.0001
4	13 (2.1)	228 (2.1)	115 (2.9)	0.015
CCI, median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0.038
Diabetes, n (%)	618 (11)	1556 (14.3)	690 (17.4)	<0.0001
Cancer, n (%)	223 (36.1)	3569 (32.8)	1138 (28.7)	<0.0001
Current smoker, n (%)	62 (10)	1413 (13)	560 (14.1)	0.013
Admission year, mean (SD)	2017 (2.03)	2016 (2.28)	2015 (2.26)	<0.0001
Surgery duration (min), mean (SD)	250 (113)	205 (93)	184 (75)	<0.0001
Surgery category, n (%)				
General surgery	111 (18)	2150 (19.8)	851 (21.5)	0.031
Gynaecology	54 (8.8)	1637 (15.1)	579 (14.6)	0.0001
Neurosurgery	129 (20.9)	1564 (14.4)	532 (13.4)	<0.0001
Ophthalmology	10 (1.6)	229 (2.1)	82 (2.1)	0.71
Orthopaedics	62 (10)	1193 (11)	400 (10.1)	0.26
Otorhinolaryngology	74 (12)	1274 (11.7)	460 (11.6)	0.95
Urology	97 (15.7)	1342 (12.3)	492 (12.4)	0.047
Vascular	23 (3.7)	732 (6.7)	271 (6.8)	0.012
Other	57 (9.2)	746 (6.9)	297 (7.5)	0.048

variable, the median change in DAOH$_{90}$ associated with a 10% point increase in FiO$_2$ was −0.05 (−1.13 to 0.02; P = 0.17). Subgroup analyses are reported in Table 2.

Secondary outcomes

The risk of surgical site infection within 90 days differed when FiO$_2$ was analysed by category. A total of 63 of 617 (10.2%), 706 of 10,867 (6.5%), and 246 of 3965 (6.2%) patients in the low, intermediate, and high FiO$_2$ categories, respectively, developed a surgical site infection. Using the high-oxygen exposure group as the reference, the OR (95% CI) for developing a surgical site infection within 90 days of surgery for intermediate FiO$_2$ was 1.05 (0.90–1.21) and for low FiO$_2$ was 1.72 (1.29–2.30). After adjustment for baseline imbalances between groups, the strength of the association between the FiO$_2$ category and occurrence of surgical site infection within 90 days was weakened but remained significantly different between the three groups; adjusted OR (95% CI) for intermediate FiO$_2$ 1.02 (0.87–1.20) and for low FiO$_2$ 1.53 (1.12–2.10). The non-linearity of this relationship between FiO$_2$ and surgical site infection

was further reflected by a non-significant OR (95% CI) for each 10% point change when FiO$_2$ was treated as a continuous variable (0.93 [0.86–1.01]).

Respiratory complications were associated with oxygen exposure when analysed according to the FiO$_2$ category. A total of 35 of 617 (5.7%), 678 of 10 867 (6.2%), and 296 of 3965 (7.5%) patients in the low, medium, and high FiO$_2$ categories, respectively, developed respiratory complications. Using the high-oxygen exposure as the reference group, the OR (95% CI) for developing a respiratory complication for intermediate FiO$_2$ was 0.82 (0.72–0.95), and for low FiO$_2$ was 0.75 (0.52–1.07). The strength of the association between the FiO$_2$ category and respiratory complication remained after adjusting for baseline imbalances (adjusted OR [95% CI] for intermediate FiO$_2$ 0.78 [0.67–0.90] and low 0.6 [0.41–0.88]). When considered as a continuous variable, the adjusted OR (95% CI) associated with a 10% point increase in FiO$_2$ was 1.17 (1.08–1.26).

A total of 139 of 617 (22.5%), 1882 of 10,867 (17.3%), and 681 of 3965 (17.2%) patients in the low, medium, and high FiO$_2$ categories, respectively, were admitted to ICU after surgery. Using the high-oxygen exposure as the reference group, the
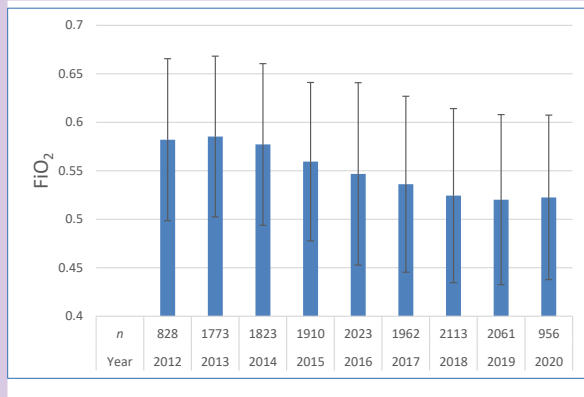
Fig 2. Mean (SD) FiO_2 administered by year of the study period. FiO_2, fraction inspired oxygen concentration; SD, standard deviation.

Discussion

Key findings

In this cohort of patients undergoing surgery at a large metropolitan hospital in New Zealand, we did not observe an association between the mean intraoperative FiO_2 and recovery from surgery as measured by $DAOH_{90}$ when patients were divided into three categories of oxygen exposure, or when mean FiO_2 was considered as a continuous variable. However, we observed an association between lower oxygen exposure and increased surgical site infection, and a dose-dependent association between increasing oxygen exposure and post-operative respiratory complications and ICU admission. The observed annual mean FiO_2 declined over the study period.

Relationship to existing knowledge

To our knowledge, no previous study has investigated the impact of different regimens of intra- or perioperative oxygen exposure on overall recovery from surgery using a primary outcome such as $DAOH_{90}$. $DAOH_{90}$ is a patient-centred outcome that has been validated across a range of medical research disciplines, including outcomes after surgery, and is expected to reflect the downstream effects of serious post-operative infections and non-infection-related complications.[13,14] The absence of an overall observed statistically significant association between intraoperative oxygen exposure and $DAOH_{90}$ in this study may be due to several reasons. First, it is possible that concentrations of inspired oxygen during surgery do not impact important aspects of recovery from surgery. It is also plausible that against the background of the multiplicity of physiological perturbations associated with surgery and anaesthesia, and within the limits of instruments and outcome measures, the impact of intraoperative oxygen exposure is not detectable. Relatedly, the duration of exposure to different concentrations of oxygen during surgery in our study population may have been insufficient to affect the recovery trajectory. Moreover, we do not know how much oxygen participants received in the recovery room or hospital ward after surgery, so we cannot exclude the possibility that the intraoperative oxygen exposure represents a minor part of a patient's cumulative exposure to oxygen during their hospital stay.

On the other hand, our failure to observe an association between intraoperative oxygen exposure and $DAOH_{90}$ may have

OR (95% CI) for post-operative ICU admission for intermediate FiO_2 was 1.01 (0.92–1.11) and for low FiO_2 was 1.40 (1.14–1.72). After adjusting for baseline imbalances, the adjusted OR (95% CI) for intermediate FiO_2 was 0.79 (0.68–0.91) and for low FiO_2 was 0.91 (0.67–1.25). When considered as a continuous variable, there was evidence of a linear relationship with each 10% increase in FiO_2 associated with an increased OR (95% CI) of admission to ICU (1.1 [1.03–1.18]). Cancer status appeared to have a moderating effect on ICU admission (interaction $P < 0.001$); in patients with cancer, there was no evidence of a relationship between ICU admission (adjusted OR [95% CI] associated with a 10% point increase in FiO_2 0.98 [0.88–1.1]). However, in patients without cancer, there was a significant linear relationship (adjusted OR [95% CI] associated with a 10% point increase in FiO_2 1.21 [1.1–1.33]).

There were no associations between FiO_2 and extrapulmonary non-infectious complications. Non-infectious complications occurred in 35 of 617 (5.7%), 678 of 10,867 (5.7%), and 296 of 3965 (5.4%) in the low, intermediate, and high oxygen categories, respectively ($P = 0.77$). There was no association between the FiO_2 category and 90-day mortality with 3 of 617 (0.5%), 131 of 10,867 (1.2%), and 36 of 3965 (0.9%) in the low, intermediate, and high oxygen categories, respectively ($P = 0.12$).

Table 2 Median regression of inspired oxygen group with point estimates (95% CI) for pre-specified subgroup analyses of the primary outcome $DAOH_{90}$. CI, confidence interval; $DAOH_{90}$, days alive and out of hospital at 90 days; PS, performance status.

	Low vs high	Intermediate vs high	Interaction P-value
Māori vs European			<0.0001
Māori	−0.84 (−2.78 to 1.1)	−0.05 (−0.51 to 0.41)	
European	0.61 (0.24 to 0.99)	0.3 (0.1 to 0.5)	
Cancer vs non-cancer surgery			<0.0001
Cancer surgery	−0.13 (−1.07 to 0.81)	−0.11 (−0.43 to 0.21)	
Non-cancer surgery	0.11 (−0.22 to 0.45)	0.02 (−0.12 to 0.17)	
Diabetes vs non-diabetes			0.37
Diabetes	−0.87 (−1.68 to −0.07)	−0.15 (−0.44 to 0.14)	
No diabetes	−0.06 (−0.38 to 0.26)	−0.07 (−0.17 to 0.03)	
ASA-PS 1 or 2 vs 3 or 4			<0.0001
ASA 1 or 2	−0.1 (−0.44 to 0.24)	0.06 (−0.09 to 0.21)	
ASA 3 or 4	1.01 (0.12 to 1.9)	0.26 (−0.06 to 0.58)	

occurred because exposure to different concentrations of oxygen could increase the risk of some post-operative complications while reducing the risk of others, and therefore balance the impact of individual differences on the primary outcome. The two most frequently observed post-operative complications were surgical site infection and post-operative respiratory complications, and negative and positive associations with increasing FiO_2 were observed with these complications, respectively.

We observed a statistically significant dose-dependent increase in respiratory complications with increasing oxygen exposure, which remained after adjusting for baseline imbalances between groups. While this finding may be the result of residual confounding whereby modelling of baseline covariates of respiratory disease inadequately adjusted for the risk of respiratory complications, the association between liberal oxygen exposure and respiratory system injury is biologically plausible,[15] and has been reported previously. A cohort study of 73,922 patients reported a dose-dependent association between intraoperative FiO_2 and major post-operative respiratory complications including respiratory failure, need for re-intubation, pneumonia, and pulmonary oedema.[9] Similarly, a cohort study of 350,647 participants undergoing surgery of at least 120-min duration compared patients in the 75th centile for intraoperative oxygen with those in the 25th centile and reported a 14% (95% CI 12%–16%) greater odds of lung injury with higher oxygen exposure.[10] In contrast, we observed an association between surgical site infection and lower oxygen exposure. Although randomised controlled trials have yielded conflicting findings about whether liberal perioperative oxygen therapy reduces surgical site infection,[16–18] the association between lower perioperative oxygen administration and increased surgical site infection has been reported in previous non-randomised studies[19,20] and some randomised trials.[21–23] A balancing effect due to this increase in surgical site infection and the decrease in post-operative respiratory complications may explain the absence of a difference in $DAOH_{90}$ between FiO_2 exposure groups.

After adjusting for baseline covariates, post-operative ICU admission was associated with high-category oxygen exposure compared with intermediate-category oxygen exposure. This may be due to the increased rate of post-operative respiratory complications that was observed in the high-oxygen category group. Patients who sustain post-operative respiratory complications and require noninvasive or invasive ventilation support are likely to receive this in the ICU in the New Zealand healthcare setting. Alternatively, this finding may be explained by residual confounding.

Implications for practice

At a population level, the beneficial effects of a particular regimen of perioperative oxygen therapy on recovery may be partially balanced by other harmful effects. Nevertheless, impacts on specific outcomes may inform the management of individual patients undergoing surgery under general anaesthesia. For example, lower FiO_2 may be more advantageous for patients with known significant respiratory comorbidity who may be at an increased risk of post-operative respiratory complications, while higher oxygen therapy may be preferable for patients at an increased risk of surgical site infection, such as those with diabetes and microvascular disease. Large clinical trials could further evaluate these hypotheses.

Study limitations

Given the retrospective observational study design, there is a high risk of residual confounding in the observed associations between intraoperative FiO_2 and recovery from surgery. For example, the association between the high FiO_2 category and post-operative respiratory complications may be due to a systematic association between increased FiO_2 and greater severity of respiratory disease that remained after adjusting for baseline covariates. While covariates of ASA-PS, smoking status, BMI, CCI, intraoperative PEEP, and type of surgery and duration of surgery were included in the logistic regression model, we did not include individual baseline respiratory comorbidities or measures of respiratory disease severity.

All data in this study were obtained from routinely collected administrative data and AIMS, so it is difficult to assess their completeness, reliability, and validity. For example, missing comorbidity data codes in the National Minimum Dataset would have resulted in a lower calculated CCI for participants, and therefore underestimated severity of baseline patient comorbidity. Nevertheless, we do not have any reason to believe that there was a systematic imbalance in data completeness between groups. In addition, there are a number of potential confounders that were not included in the analyses, such as the use of neuromuscular blocking drugs, the use of neuromuscular blocker reversal drugs and completeness of reversal of neuromuscular blockade, the use and total dose of opioids administered, and the use of regional or neuraxial anaesthesia. Relatedly, we found that a high proportion of study participants were admitted to the ICU post-operatively. We speculate that this is partly explained by the inclusion of patients admitted to the HDU under the ICU admission code. Given that we excluded patients with a surgical duration less than 2 h, we have selected a cohort of patients undergoing prolonged surgery that could reasonably be expected to have a higher rate of post-operative ICU or HDU admission than patients undergoing operations with a duration of less than 2 h.

A further limiting factor of our approach using the NMDS 'condition onset flag' is that it was not possible to know if a diagnostic code with a 'condition onset flag' occurred before or after surgery during the admission of interest. However, we submit that it would be uncommon for patients undergoing planned surgical procedures to sustain major complications before surgery, and if such complications did occur, it is likely that elective surgery would be deferred, thereby causing these patients to not be included in the study population.

Finally, given the uneven distribution of participants across the three groups of oxygen exposure, it is likely that there was reduced power to detect differences in outcomes between study groups.

Conclusions

In this retrospective cohort study of patients undergoing major surgery at a large metropolitan hospital in New Zealand, we observed associations between low intraoperative FiO_2 and the risk of surgical site infection, and a dose-dependent increase in FiO_2 and post-operative respiratory complications and admission to the ICU, which did not translate to any confounder-adjusted differences in overall recovery from surgery as measured using $DAOH_{90}$. These findings warrant further evaluation in randomised controlled trials.

Authors' contributions

Conception and design of the study; acquisition; analysis, interpretation of data, or both; drafting; or revising the article for intellectual content: All authors
Final approval of the manuscript and accountability for all aspects of the work: All authors

Declaration of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

We acknowledge Emeritus Professor Alan Merry for his contribution to the study design.

References

1. Lyons C, Callaghan M. Uses and mechanisms of apnoeic oxygenation: a narrative review. *Anaesthesia* 2019; **74**: 497−507
2. World Health Organization. *Global guidelines for the prevention of surgical site infection*. 2nd Edn. Geneva, Switzerland: World Health Organization; 2018
3. Li Puma LC, Hedges M, Heckman JM, et al. Experimental oxygen concentration influences rates of mitochondrial hydrogen peroxide release from cardiac and skeletal muscle preparations. *Am J Physiol Regul Integr Comp Physiol* 2020; **318**: R972. −R80
4. Oldman AH, Martin DS, Feelisch M, Grocott MPW, Cumpstey AF. Effects of perioperative oxygen concentration on oxidative stress in adult surgical patients: a systematic review. *Br J Anaesth* 2021; **126**: 622−32
5. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. *Circulation* 2018; **137**: 2114−24
6. McEvoy JW. Excess oxygen in acute illness: adding fuel to the fire. *Lancet* 2018; **391**: 1640−2
7. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; **391**: 1693−705
8. Yokoyama S, Hifumi T, Kawakita K, Tamiya T, Minamino T, Kuroda Y. Early hyperoxia in the intensive care unit is significantly associated with unfavorable neurological outcomes in patients with mild-to-moderate aneurysmal subarachnoid hemorrhage. *Shock* 2019; **51**: 593−8
9. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, et al. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. *Br J Anaesth* 2017; **119**: 140−9
10. McIlroy DR, Shotwell MS, Lopez MG, et al. Oxygen administration during surgery and postoperative organ injury: observational cohort study. *BMJ* 2022; **379**, e070941
11. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453−7
12. New Zealand Ministry of Health. *National minimum dataset*. Available from: https://www.health.govt.nz/publication/national-minimum-dataset-hospital-events-data-dictionary. [Accessed 27 December 2023]
13. Alexander H, Moore M, Hannam J, Poole G, Bartlett A, Merry A. Days alive and out of hospital after laparoscopic cholecystectomy. *ANZ J Surg* 2022; **92**: 2889−95
14. Jerath A, Austin PC, Wijeysundera DN. Days alive and out of hospital: validation of a patient-centered outcome for perioperative medicine. *Anesthesiology* 2019; **131**: 84−93
15. Alva R, Mirza M, Baiton A, et al. Oxygen toxicity: cellular mechanisms in normobaric hyperoxia. *Cell Biol Toxicol* 2023; **39**: 111−43
16. de Jonge S, Egger M, Latif A, et al. Effectiveness of 80% vs 30−35% fraction of inspired oxygen in patients undergoing surgery: an updated systematic review and meta-analysis. *Br J Anaesth* 2019; **122**: 325−34
17. Mattishent K, Thavarajah M, Sinha A, et al. Safety of 80% vs 30−35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis. *Br J Anaesth* 2019; **122**: 311−24
18. Ferrando C, Aldecoa C, Unzueta C, et al. Effects of oxygen on post-surgical infections during an individualised perioperative open-lung ventilatory strategy: a randomised controlled trial. *Br J Anaesth* 2020; **124**: 110−20
19. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* 1997; **132**: 997−1004. discussion 1005
20. Kotani N, Hashimoto H, Sessler DI, et al. Supplemental intraoperative oxygen augments antimicrobial and proinflammatory responses of alveolar macrophages. *Anesthesiology* 2000; **93**: 15−25
21. Greif R, Akca O, Horn EP, Kurz A, Sessler DI, Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000; **342**: 161−7
22. Belda FJ, Aguilera L, Garcia de la Asuncion J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA* 2005; **294**: 2035−42
23. Myles PS, Carlisle JB, Scarr B. Evidence for compromised data integrity in studies of liberal peri-operative inspired oxygen. *Anaesthesia* 2019; **74**: 573−84

Handling editor: Phil Hopkins