ANESTHESIOLOGY

Supplemental Intraoperative Oxygen and Long-term Mortality

Subanalysis of a Multiple Crossover Cluster Trial

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ABSTRACT

Background: Whether supplemental oxygen worsens long-term mortality remains unclear, with contradictory trial results. The authors therefore tested the hypothesis that supplemental oxygen (80% *vs.* 30%) increases the hazard for long-term mortality.

Methods: The authors conducted a *post hoc* analysis of a large multiple crossover cluster trial in which more than 5,000 colorectal surgeries on 4,088 adults were allocated to receive either 30% or 80% inspired oxygen during general anesthesia. The authors assessed the effect of 80% *versus* 30% target-inspired oxygen on long-term mortality and calculated Kaplan–Meier survival estimates. Analysis was restricted to patients with a home address in Ohio because the authors could obtain reliable vital status information from the Ohio Department of Health (Columbus, Ohio) for them.

Results: A total of 3,471 qualifying colorectal surgeries performed in 2,801 patients were analyzed, including 1,753 (51%) surgeries in 1,577 patients given 80% oxygen and 1,718 surgeries in 1,551 patients given 30% oxygen. The observed incidence of death after a median of 3 yr was 13% (234 of 1,753) in the 80% oxygen group and 14% (245 of 1,718) in the 30% oxygen group. The estimated hazard ratio for mortality was 0.94 (95% CI, 0.78 to 1.13; $P = 0.493$).

Conclusions: In this *post hoc* analysis of a large, controlled trial, supplemental oxygen did not increase postoperative mortality.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- It remains unclear whether supplemental intraoperative oxygen (80% vs. 30%) worsens postoperative mortality.

What This Article Tells Us That Is New

- In a *post hoc* analysis of a controlled trial of 3,471 colorectal surgeries, the incidence of death after a median of 3 yr of follow-up was 13% with 80% oxygen and 14% with 30% oxygen, giving an estimated hazard ratio for mortality of 0.94 (95% CI, 0.78 to 1.13; $P = 0.493$). Supplemental oxygen does not increase mortality.

Surgical site infections and wound-related complications are common and serious. While the overall incidence of surgical site infections is 1 to 3%,[1–3] it is 10% or more after colorectal surgery.[4–6] The primary defense against bacterial infection is oxidative killing by neutrophils, which requires molecular tissue oxygen.[7] Increasing inspired oxygen is an easy and effective way to augment tissue oxygen.[8,9] The theory that supplemental oxygen might reduce the risk of surgical wound infection led to two decades of studies. While initial trials were supportive,[9,10] subsequent large trials were not,[11,12] and a recent meta-analysis of reliable trials suggests that supplemental oxygen at most slightly reduces the perioperative infection risk.[13]

The second largest trial of supplemental oxygen (Supplemental Oxygen and Complications After Abdominal Surgery [PROXI] trial; n = 1,400) by Meyhoff *et al.* reported that 80% inspired oxygen did not decrease the incidence of wound infections,[11] but increased the hazard for mortality by 30% over a median of 2.3 postoperative yr.[14] Curiously, increased mortality was restricted to cancer patients.[14] Postulated explanations include increased tumor growth as a result of hyperoxia-induced neovascularization, increased erythropoietin release, and DNA damage by oxygen-triggered reactive oxygen species.[15–19] However, further analysis of the PROXI trial revealed that new or recurrent cancers occurred at similar rates in patients given 30% and 80% oxygen.[20] Although new or recurrent cancers occurred slightly earlier in patients given 80% oxygen, the magnitude was insufficient to explain the excess mortality in the 80% oxygen group. In contrast, a reanalysis of several trials showed virtually identical long-term mortality rates over median follow-up periods ranging from 4.3 yr to 12.8 yr in 927 patients who were randomized to 30% or 80% intraoperative oxygen.[21]

The extent to which supplemental oxygen might promote long-term mortality therefore remains unclear. By far the largest controlled trial of supplemental oxygen enrolled 4,088 patients who had 5,167 surgeries from January 2013

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to March 2016.[12] Sufficient time has now elapsed to reliably estimate long-term mortality in participating patients. We therefore tested the primary hypothesis that supplemental oxygen (80% *vs.* 30%) increases the risk of long-term mortality. Secondarily, we evaluated whether the effect of supplemental oxygen on long-term mortality differs in patients who did and did not have colorectal cancer.

Materials and Methods

We conducted a *post hoc* analysis of a large, single-center multiple crossover cluster trial in which adults having colorectal surgery were allocated to receive either 30% or 80% inspired oxygen (F_{IO_2}) during general anesthesia. In the original trial, we tested the primary hypothesis that supplemental oxygen (80% *vs.* 30% as tolerated) reduces the risk of a 30-day collapsed composite (one or more) of surgical site infection, healing-related wound complications, and mortality. The underlying trial was approved by the Cleveland Clinic Institutional Review Board (12-891; Cleveland, Ohio) with a waived requirement for informed consent and was registered at ClinicalTrials.gov (NCT01777568) on January 29, 2013. The principal investigator for registration was Andrea Kurz.

The current subanalysis was also approved with a waived requirement for informed consent by the Cleveland Clinic Institutional Review Board. A detailed statistical analysis plan was developed *a priori* and approved by the Cleveland Clinic Institutional Review Board. The primary outcome and several subanalyses from the original trial have been published, all focused on short-term outcomes.[22–24] The statisticians were not blinded to treatment group assignment.

In brief, all patients who had surgery in a designated operating room suite at the Cleveland Clinic Main Campus (Cleveland, Ohio) over a 39-month period from 2013 to 2016 participated in the underlying trial. However, the analysis was restricted to patients who had colorectal surgery lasting at least 2 h. The amount of intraoperative inspired oxygen was randomly assigned for the initial 2 weeks, and then alternated every 2 weeks between 30% and 80%. No other aspects of ventilation were controlled, nor was postoperative F_{IO_2}. As a safety measure, clinicians were instructed to give enough oxygen to maintain oxygen saturation measured by pulse oximetry at or above 95%. During anesthetic induction and emergence, 100% inspired oxygen was allowed.

In the underlying trial, patients with missing oxygen data or baseline covariables and reoperations during the same hospitalization were excluded from analysis. We further restricted our primary analysis to patients with a home address in Ohio because we could obtain reliable vital status data from the Ohio Department of Health (Columbus, Ohio) for them. Ohio Death Index data are maintained by Ohio Department of Health and were updated to December 12, 2018, when we accessed the registry. Vital status and follow-up dates were identified using Cleveland Clinic Epic system and Ohio Death Index: (1) from the Epic system, we extracted patient death information and the latest office visit date; and (2) for patients with a home address in Ohio, we also determine their vital status from the Ohio Death Index. When death was not recorded in the Ohio index, statistical analyses were censored at the latest office visit date.

Statistical Methods

We descriptively compared the 80% and 30% oxygen patients based on demographic, baseline, and procedural variables using standard descriptive statistics and the absolute standardized difference. The absolute standardized difference was calculated as the absolute difference in means or proportions divided by the pooled SD, and any imbalanced factor with absolute standardized difference greater than 0.10 was adjusted for in the analyses.

We assessed the effect of 80% *versus* 30% target-inspired oxygen on long-term mortality using a Cox proportional hazards regression model incorporating patient as a random effect to account for correlation within some patients across multiple surgeries. Kaplan–Meier survival estimates were calculated. When patients were included more than once, previous surgeries were censored the day before the date of the subsequent surgery. Since some patients who participated several times received different treatments, we conducted sensitivity analyses by retaining only the first or last surgery or all surgeries to assess the robustness of our statistical methods. In the primary analysis, we used several methods to assess the proportional hazards assumption, including testing the interaction between treatment and log (time), a correlation test based on the weighted Schoenfeld residuals, a Supremum test, and a visual display of log (hazards) *versus* time.

We assessed heterogeneity of the treatment effect across levels of selected baseline variables using Cox proportional hazards regression and testing the treatment-by-variable interaction. Baseline factors of interest, assessed in separate models, included type of surgery (colorectal resection *vs.* others), age (less than 60 *vs.* greater than or equal to 60 yr), sex (female *vs.* male), American Society of Anesthesiologists (ASA; Schaumburg, Illinois) physical status (I to II *vs.* III to V), primary diagnosis (cancer *vs.* other), body mass index (less than 30 kg/m^2 *vs.* greater than or equal to 30 kg/m^2), current smoking (yes *vs.* no), and laparoscopic surgery (yes *vs.* no). The treatment effect was assessed within levels of each factor.

As this study represents a *post hoc* analysis using available data from the original trial, we did not conduct an *a priori* power calculation. In a *post hoc* power calculation, we assumed that a hazard ratio of 1.2 or stronger was clinically important, indicating that patients in the treatment arm (or control group, since the test was two-tailed) had 20% higher chance of dying at any time during follow-up *versus* control. Using the estimated survival of 77% at 6 yr in our control group as reference, and assuming survival times followed an exponential distribution, with the attained sample size of 3,471, we could only detect a hazard ratio of 1.24 or stronger with 80% power.

Results are reported as hazard ratios. A two-sided significance level of 0.05 was used for the overall assessment. The significance criterion for each interaction was set to 0.05/8 = 0.0062. SAS 9.4 software (SAS Institute, USA) was used.

Results

The underlying trial was conducted at the Cleveland Clinic Main Campus from January 28, 2013, to March 11, 2016. The original trial analyzed 4,088 patients who had 5,167 surgeries and assessed the treatment effect on a 30-day composite of deep tissue or organ-space surgical site infection, healing-related wound complications, and mortality. For the primary analysis of this *post hoc* analysis, a total of 3,471 qualifying colorectal surgeries performed in 2,801 Ohio patients were analyzed, including 1,753 (51%) surgeries in 1,577 patients assigned to 80% oxygen and 1,718 surgeries in 1,551 patients assigned to 30% oxygen (fig. 1). Among the 2,801 patients qualifying for the current analysis, 457 were enrolled twice and 101 were enrolled three or more times; 327 patients received different treatments.

The 80% and 30% oxygen groups were well balanced on most of demographic, baseline, and procedural variables (absolute standardized difference less than 0.10, table 1) except smoking (absolute standardized difference, 0.110) and time-weighted average intraoperative heart rate (absolute standardized difference, 0.119). Overall mortality was 13.8% after a median (25th, 75th percentiles) follow-up period of 3.2 (0.5, 4.9) yr. We did not find an effect of 80% *versus* 30% oxygen on long-term mortality, with an estimated hazard ratio of 0.94 (95% CI, 0.78 to 1.13; $P = 0.493$; table 2, fig. 2). After 5 yr, the estimated survival rate was 80% (95% CI, 78 to 83%) in patients assigned to 80% oxygen and 80% (95% CI, 77 to 82%) in those assigned to 30% oxygen. For the primary analysis, Kaplan–Meier curves were close to each other and nonoverlapping. While the treatment-by-time interaction was significant ($P = 0.019$), the other two proportional hazards tests were not (correlation test based on the weighted Schoenfeld residuals, $P = 0.202$; and supremum test, $P = 0.233$). We thus concluded that there was no clinically meaningful violation of the proportional hazard assumption.

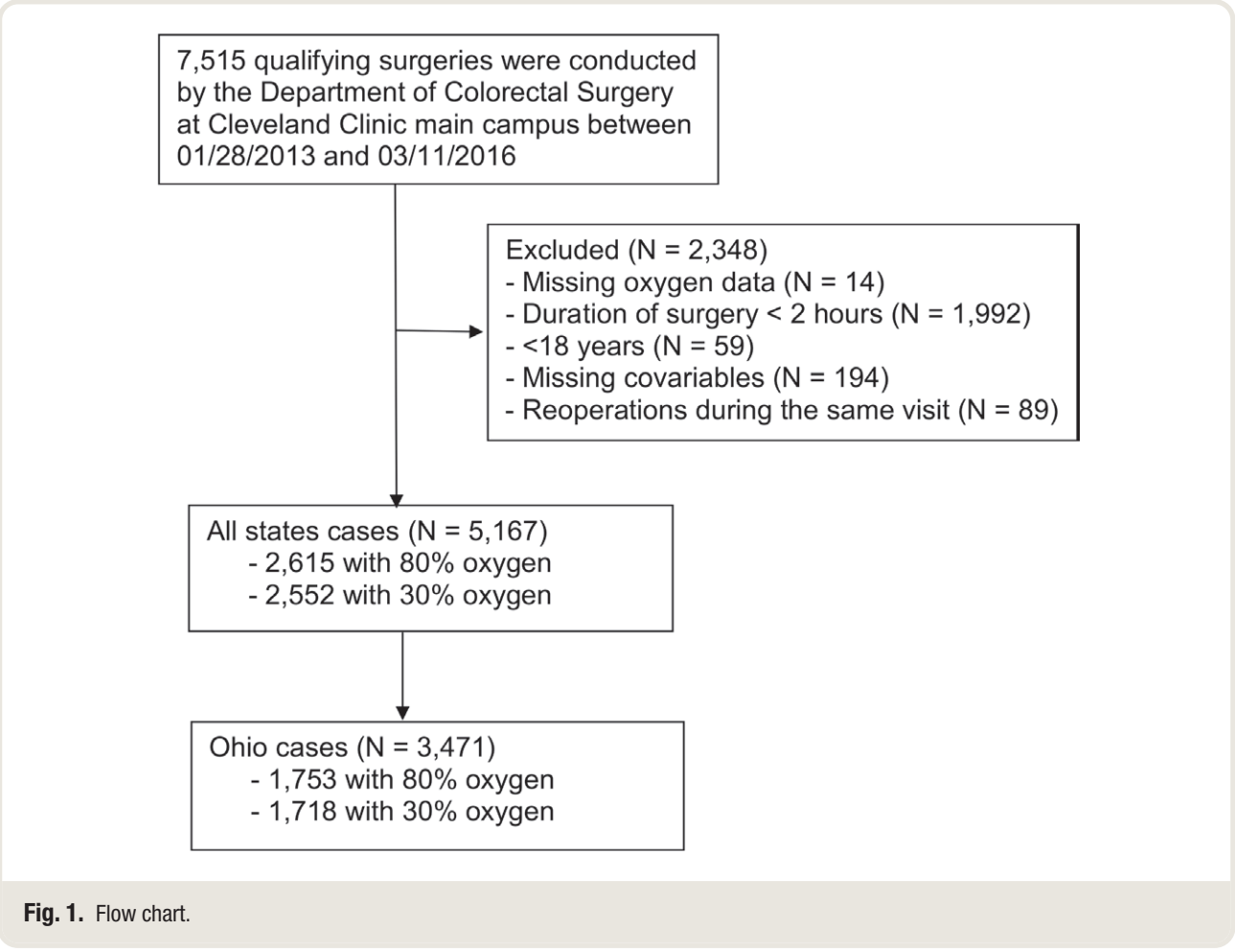

Fig. 1. Flow chart.

Table 1. Baseline and Procedural Variables for Ohio Patients (N = 3,471)

Variables	80% Oxygen (N = 1, 753)	30% Oxygen (N = 1, 718)	Absolute Standardized Difference*
Age, yr	54 ± 17	53 ± 17	0.038
Sex, No. (%)			0.015
Female	902 (51)	897 (52)	
Male	851 (49)	821 (48)	
Race, No. (%)			0.056
White	1560 (89)	1498 (87)	
Black	163 (9)	187 (11)	
Other	30 (2)	33 (2)	
Body mass index, kg/m^2	26 [23, 31]	27 [23, 31]	0.015
Smoking status, No. (%)			0.110
Current smoker	235 (13)	170 (10)	
Ex-smoker	517 (30)	521 (30)	
Never smoker	1001 (57)	1027 (60)	
ASA physical status, No. (%)			0.007
I	8 (0)	7 (0)	
II	517 (30)	501 (29)	
III	1077 (61)	1062 (62)	
IV	149 (9)	148 (9)	
V	2 (0)	0 (0)	
Medical history, No. (%)			
Congestive heart failure	71 (4)	76 (4)	0.019
Vascular disease	69 (4)	73 (4)	0.016
Pulmonary circulation disease	85 (5)	67 (4)	0.046
Peripheral vascular disease	129 (7)	111 (7)	0.035
Hypertension, uncomplicated	618 (35)	607 (35)	0.002
Hypertension, complicated	83 (5)	80 (5)	0.004
Paralysis	20 (1)	16 (1)	0.021
Other neurologic disorders	84 (5)	106 (6)	0.061
Chronic pulmonary disease	281 (16)	266 (16)	0.015
Diabetes without chronic complications	176 (10)	164 (10)	0.017
Diabetes with chronic complications	49 (3)	60 (4)	0.040
Hypothyroidism	179 (10)	192 (11)	0.031
Renal failure	98 (6)	97 (6)	0.002
Liver disease	50 (3)	53 (3)	0.014
Peptic ulcer disease (bleeding)	2 (0)	1 (0)	0.019
AIDS	3 (0)	1 (0)	0.033
Lymphoma	37 (2)	35 (2)	0.005
Metastatic cancer	147 (8)	161 (9)	0.035
Solid tumor without metastasis	381 (22)	311 (18)	0.091
Rheumatoid arthritis/collagen vascular disease	85 (5)	84 (5)	0.002
Coagulopathy	144 (8)	124 (7)	0.037
Obesity	383 (22)	421 (25)	0.063
Weight loss	523 (30)	512 (30)	0.001
Fluid and electrolyte disorders	815 (47)	798 (46)	0.001
Chronic blood loss anemia	57 (3)	56 (3)	0.000
Deficiency anemias	432 (25)	450 (25)	0.036
Alcohol abuse	37 (2)	35 (2)	0.005
Drug abuse	54 (3)	55 (3)	0.007
Psychoses	108 (6)	99 (6)	0.017
Depression	343 (19)	318 (19)	0.027
Primary diagnosis, No. (%)			0.062
Cancer	833 (48)	788 (46)	
Crohn disease	280 (16)	280 (16)	
Diverticulitis	168 (10)	169 (10)	
Ostomy	135 (8)	127 (7)	
Fistula	115 (6)	131 (8)	
Hernia	41 (2)	44 (3)	
Other	181 (10)	179 (10)	
Preoperative oral antibiotic, No. (%)	811 (46)	804 (47)	0.011
Preoperative bowel preparation medication, No. (%)	376 (21)	343 (20)	0.037
Type of surgery, No. (%)			0.074

(*Continued*)

Table 1. (*Continued*)

Variables	80% Oxygen (N = 1, 753)	30% Oxygen (N = 1, 718)	Absolute Standardized Difference*
Colorectal resection	951 (54)	896 (52)	
Lower gastrointestinal therapeutic procedures	523 (30)	525 (31)	
Small bowel resection	99 (6)	104 (6)	
Exploratory laparotomy	35 (2)	48 (3)	
Excision	30 (2)	29 (2)	
Laparoscopy	35 (2)	36 (2)	
Hernia repair	39 (2)	39 (2)	
Ileostomy and other enterotomy	21 (1)	26 (1)	
Colostomy	20 (1)	15 (1)	
Laparoscopic surgery (*vs.* open or converted), No. (%)	508 (29)	469 (27)	0.037
Duration of surgery, h	4.2 ± 1.7	4.2 ± 1.8	0.030
Regional block, No. (%)	42 (2)	59 (3)	0.062
Spinal or epidural anesthesia, No. (%)	133 (8)	144 (8)	0.029
Attending anesthesiologist,‡ No. (%)			—†
A	231 (13)	228 (13)	
B	241 (14)	223 (13)	
C	73 (4)	101 (6)	
D	82 (5)	51 (3)	
E	39 (2)	58 (3)	
Operating room number, No. (%)			0.076
#47	388 (22)	357 (21)	
#48	371 (21)	348 (20)	
#50	310 (18)	320 (19)	
#46	259 (15)	253 (15)	
#45	256 (15)	265 (15)	
#49	93 (5)	112 (6)	
#40–44	76 (4)	63 (4)	
Intraoperative management			
Time-weighted average of esophageal temperature, °C	36.0 ± 0.6§	36.0 ± 0.6‖	0.061
Esophageal temperature at end of case, °C	36.4 [35.9, 36.8]§	36.4 [35.9, 36.8]‖	0.007
Time-weighted average of MAP, mmHg	86 ± 9	85 ± 9	0.096
Time-weighted average of HR, beats/min	76 ± 11	78 ± 12	0.119
Amount of anesthetic gas (MAC), h	2.9 [2.0, 4.2]#	2.9 [2.0, 4.1]**	0.019
Fraction of inspired oxygen, %	80 [78, 82]	39 [35, 47]	3.121
Time-weighted average of P_{ETCO_2}, mmHg	35 ± 2	35 ± 2	0.033
Time-weighted average of glucose, mg/dl	141 [121, 164]††	140 [118, 164]‡‡	0.053
Crystalloid volume, l	2.7 [2, 3.5]	2.8 [2, 3.6]	0.028
Laparoscopic surgery	2.8 [2.2, 3.4]	2.8 [2.2, 3.5]	
Open surgery	2.6 [1.8, 3.6]	2.7 [1.8, 3.6]	
Colloid volume, l	0 [0, 0.25]	0 [0, 0.5]	0.094
Estimated blood loss, ml	100 [50, 200]	100 [50, 250]	0.050
Blood transfusion, No. (%)	142 (8)	144 (8)	0.010
Amount of blood transfusion among patients who were transfused, l	0.7 [0.4, 1.0]	0.7 [0.4, 1.0]	0.012

Summary statistics (presented as percentage of patients, mean ± SD, or median [25th, 75th percentiles] for factors, symmetric continuous variables, and skewed continuous variables, respectively).

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD. Any baseline or procedural variables with an absolute standardized difference greater than 0.10 was considered to be imbalanced and would be adjusted for in the analysis. †Absolute standardized difference was not calculated due to too many categories (among 64 anesthesiologists). ‡Five attending anesthesiologists (of 64) are listed due to the limited space. §A total of 80 cases have missing data. ‖A total of 58 patients have missing data. #Two cases have missing data. **Five cases have missing data. ††A total of 1,239 cases have missing data. ‡‡A total of 1,178 cases have missing data.

AIDS, acquired immune deficiency syndrome; ASA, American Society of Anesthesiologists; HR, heart rate; MAC, minimal alveolar concentration; MAP, mean arterial blood pressure; P_{ETCO_2}, end-tidal pressure of carbon dioxide.

There were also no differences in the relative effects of oxygen in cancer and noncancer patients (fig. 3). The effect of oxygen on mortality also did not depend on the type of surgery, age, body mass index, smoking status, ASA physical status, primary diagnosis, or surgical approach (fig. 3).

Results were similar when the analysis was restricted to only the first or last surgery or including patients from all states (appendix table A1). Demographic, baseline, and procedural variables are shown in appendix table A2 for the first surgery of Ohio patients, and in appendix table A3 for the last surgery of Ohio patients.

Table 2. Primary Results: Effect of 80% *versus* 30% Oxygen Supplement on Long-term mortality in Ohio Patients (N = 3,471 Surgeries)

	N	Long-term Mortality (%)	Median Follow-up (yr) [25th, 75th Percentiles]	2-yr Survival % (95% CI)	5-yr Survival % (95% CI)	Hazard Ratio (95% CI)	*P* Value
Primary analysis (all operations)*							0.493
30% Oxygen	1,718	245 (14)	3.1 [0.5, 4.9]	90% (88–92%)	80% (77–82%)	Reference = 1	
80% Oxygen	1,753	234 (13)	3.2 [0.5, 4.9]	91% (89–92%)	80% (78–83%)	0.94 (0.78–1.13)	
Sensitivity analyses							
***Only the first operation per patient*†**							0.615
30% Oxygen	1,391	244 (18)	4.1 [1.7, 5.4]	90% (88–92%)	80% (77–82%)	Reference = 1	
80% Oxygen	1,410	235 (17)	4.1 [1.6, 5.4]	90% (88–92%)	80% (78–83%)	0.95 (0.80–1.14)	
***Only the last operation per patient*‡**							0.681
30% Oxygen	1,389	245 (18)	4.0 [1.5, 5.2]	89% (88–91%)	79% (77–82%)	Reference = 1	
80% Oxygen	1,412	234 (17)	4.0 [1.4, 5.2]	90% (88–91%)	80% (77–82%)	0.96 (0.80–1.15)	

*Multivariable random-effects Cox proportional hazards regression adjusting for smoking status and time-weighted average of intraoperative heart (*i.e.,* imbalanced with absolute standardized difference greater than 0.1 in table 1), and incorporating cluster-specific random effects of multiple surgeries within patients. †Multivariable random-effects Cox proportional hazards regression adjusting for smoking status, time-weighted average of intraoperative mean arterial pressure (*i.e.,* imbalanced with absolute standardized difference greater than 0.1 in table A2). ‡Multivariable random-effects Cox proportional hazards regression adjusting for time-weighted average of intraoperative heart rate, smoking status, and intraoperative colloids infusion (*i.e.,* imbalanced with absolute standardized difference greater than 0.1 in table A3).

Discussion

We conducted a *post hoc* analysis of a single-center crossover cluster trial. The original trial tested the hypothesis that supplemental oxygen decreases the incidence of postoperative wound infections and infection-related complications.[12] The use of a novel crossover cluster design allowed rapid enrollment of approximately 5,100 surgeries on 4,088 patients. As might be expected for a subset with about 2,800 patients who had more than 3,400 operations, there was remarkably good balance between the groups on a long list of observed potential confounding factors. Long-term mortality hazard was nearly identical in patients assigned to 30% and 80% intraoperative oxygen. Our results are therefore inconsistent with the theory that high intraoperative inspired oxygen promotes long-term mortality after colorectal surgery.

Our findings are consistent with those of Podolyak *et al.*, who analyzed long-term mortality in more than 900 patients who participated in various randomized trials conducted more than a decade ago.[21] Supplemental oxygen did not increase long-term mortality, with an overall site-stratified

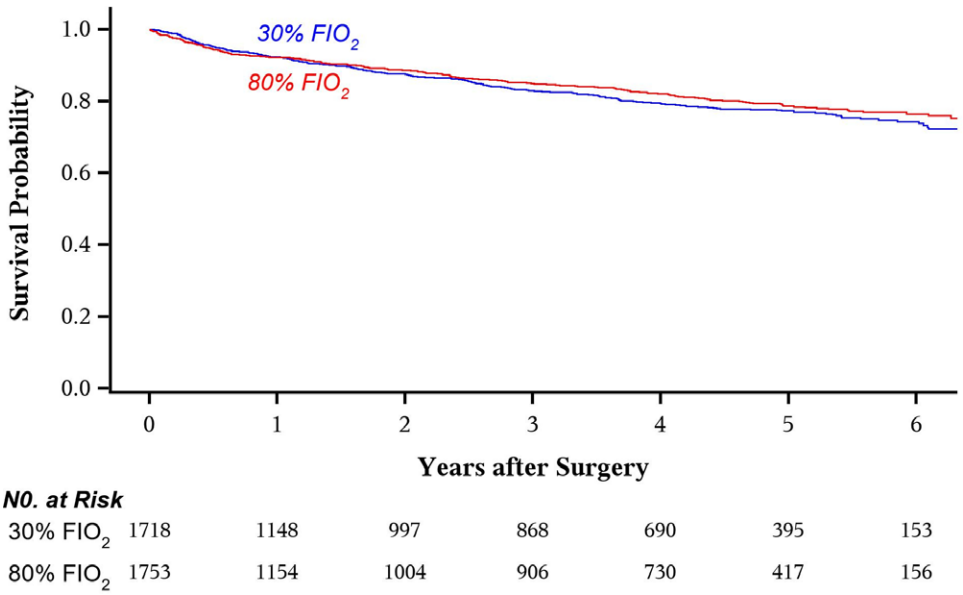

Fig. 2. Kaplan–Meier survival curve estimates comparing patients assigned to receive 80% and 30% intraoperative inspired oxygen. The hazard ratio was an estimated 0.94 (95% CI, 0.78 to 1.13; $P = 0.493$).

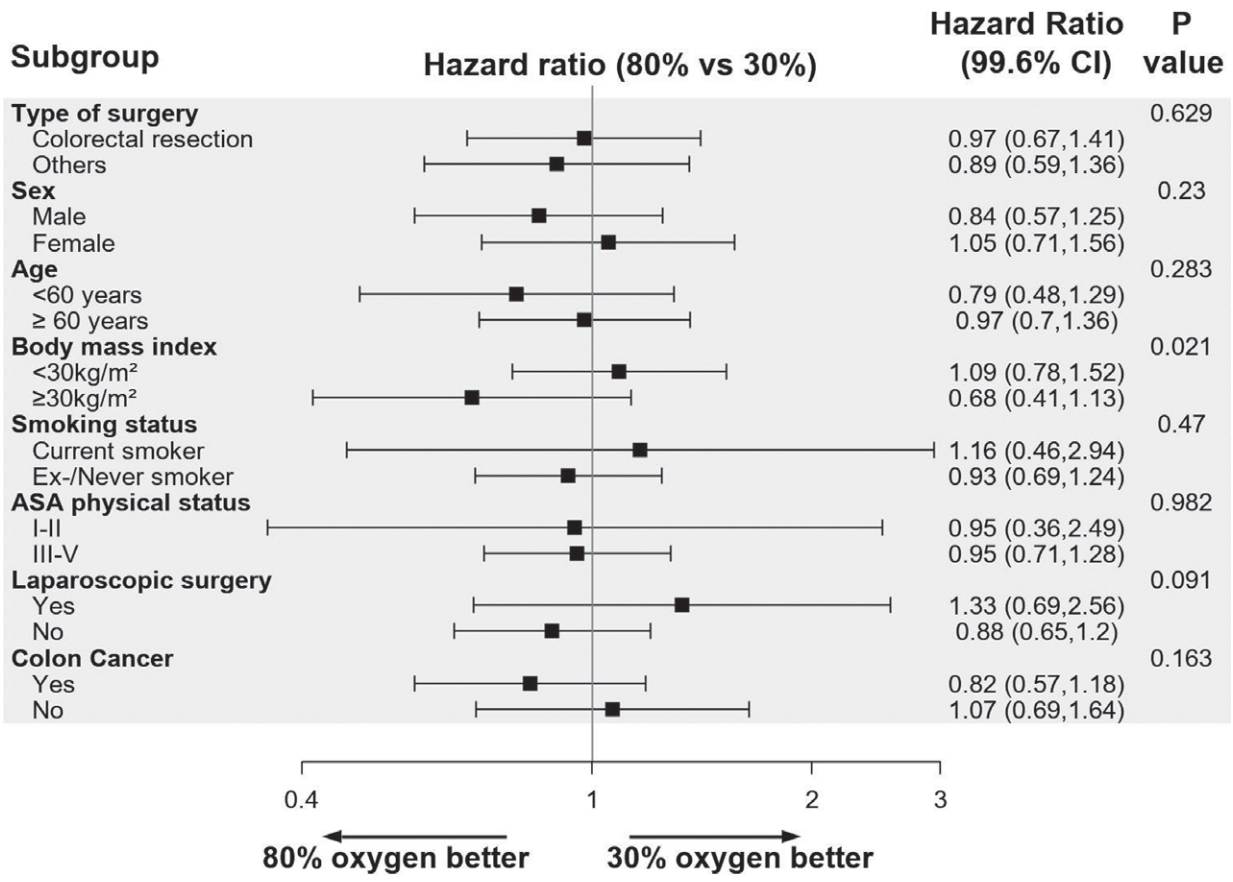

Fig. 3. Hazard ratios of the primary outcome of long-term mortality in patients assigned to 80% *versus* 30% oxygen within the levels of the selected factors. The significance criterion for each interaction was set to 0.05/8 = 0.0062, and the significance criterion was 0.0031 for each comparison (*i.e.,* 0.05 of 16), and thus 99.6% CIs are plotted. None of the interactions between the treatment and these factors was statistically significant on the primary outcome (all $P > 0.0062$).

hazard ratio of 0.93 (95% CI, 0.72 to 1.20).[21] Our current results and those of Podolyak *et al.*[21] contrast with those reported by the PROXI investigators, who randomized 1,400 patients to 30% or 80% inspired intraoperative oxygen. The primary outcome was surgical site infection, which did not differ. In a secondary analysis, mortality was substantially increased in patients given supplemental intraoperative oxygen (hazard ratio, 1.31 [95% CI, 1.03 to 1.66]).[14]

Why the PROXI results are discrepant remains unclear. Mortality in the PROXI trial was evaluated over a median of 2.3 yr *versus* 4.7 yr in our current analysis, and a range between 3.6 and 13.6 yr in the analysis of Podolyak *et al.* However, longer follow-up periods in the more recent articles[21] do not explain reported mortality differences since the hazard ratios were similar throughout the follow-up periods. There were substantive differences among the three analyses in terms of patient age, the fractions of laparoscopic and emergency procedures, and the types of procedures. However, subgroup analyses in our current study showed no significant interaction with type of surgery, age, body mass index, smoking, ASA physical status, or surgical approach. It therefore seems unlikely that any of these factors greatly influences the relative effect of inspired oxygen concentration on long-term mortality or explains why mortality differed with oxygen concentration in PROXI but not in subsequent reports.

In the PROXI trial, supplemental oxygen increased long-term mortality specifically in a subgroup of 352 cancer patients. The investigators proposed that high F_{IO_2} increased long-term mortality in cancer patients by promoting the growth of circulating tumor cells after potentially curative surgery. In a subsequent substudy of the PROXI trial, however, the authors could not demonstrate that 80% oxygen increases the incidence of new cancer or cancer recurrence. Although new or recurrent cancers occurred 100 days earlier in patients receiving supplemental oxygen, earlier recurrence was insufficient to explain the excess mortality in cancer patients.[20] In our study, 80% inspired oxygen did not augment long-term mortality in 995 cancer patients, nor did it in 451 cancer patients in the study by Podolyak *et al.*[21] Data from 1,446 patients, therefore, do not

support the theory that supplemental oxygen has long-term toxicity specific to cancer surgical patients.

We used the Ohio Death Index from the Ohio Department of Health to evaluate mortality. The Ohio Death Index has high validity for vital status.[25] However, 31% of patients in the underlying trial lived elsewhere. The analysis population was thus restricted to 2,801 patients. Nonetheless, we report by far the largest trial of inspired intraoperative oxygen and mortality.

A partial limitation of our analysis is that approximately 20% of patients had more than one operation. For these patients, previous surgeries were censored the day before the date of the next surgery since some of them might receive different treatments. We adjusted for the potential within-patient correlation by including patient as a random effect. An advantage of retaining all cases during the study period is that we gained power and perhaps generalizability. However, we also conducted sensitivity analyses restricted to the first or last surgery; the results were similar, indicating that our statistical methods were robust. An additional limitation is that the inspired oxygen concentration in patients assigned to receive 30% was actually given with a median of 39% [Q1, Q3: 35%, 47%]. However, the higher concentration was not a protocol deviation because clinicians were instructed to give sufficient oxygen to maintain an oxygen saturation of at least 95%. Many of our patients needed more oxygen because they were obese and/or required Trendelenburg positioning, which decreased their saturation.

We assumed that a hazard ratio less than or equal to 0.83 or greater than or equal to 1.2 was clinically important. The 95% CI of the hazard ratio for the primary analysis was within 0.78 and 1.13, which was fairly narrow, and the upper limit of 1.13 was not beyond what the study was designed to detect (a hazard ratio of 1.2 or more). Therefore, it allows us to make a fairly strong negative conclusion.

In summary, we performed a *post hoc* analysis of a large crossover cluster trial and evaluated whether intraoperative supplemental oxygen causes long-term mortality. Supplemental oxygen did not increase postoperative mortality overall, or in cancer patients, and can be safely used when deemed appropriate.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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References

1. Owens CD, Stoessel K: Surgical site infections: Epidemiology, microbiology and prevention. J Hosp Infect 2008; 70(suppl 2):3–10
2. Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA, Crosby C: Impact of surgical site infection on healthcare costs and patient outcomes: A systematic review in six European countries. J Hosp Infect 2017; 96:1–15
3. Waltz PK, Zuckerbraun BS: Surgical site infections and associated operative characteristics. Surg Infect (Larchmt) 2017; 18:447–50
4. Martin D, Hübner M, Moulin E, Pache B, Clerc D, Hahnloser D, Demartines N, Grass F: Timing, diagnosis, and treatment of surgical site infections after colonic surgery: prospective surveillance of 1263 patients. J Hosp Infect 2018; 100:393–9
5. Paulson EC, Thompson E, Mahmoud N: Surgical site infection and colorectal surgical procedures: A prospective analysis of risk factors. Surg Infect (Larchmt) 2017; 18:520–6
6. Gomila A, Carratalà J, Biondo S, Badia JM, Fraccalvieri D, Shaw E, Diaz-Brito V, Pagespetit L, Freixas N, Brugués M, Mora L, Perez R, Sanz C, Arroyo N, Iftimie S, Limón E, Gudiol F, Pujol M; VINCat Colon Surgery Group: Predictive factors for early- and late-onset surgical site infections in patients undergoing elective colorectal surgery. A multicentre, prospective, cohort study. J Hosp Infect 2018; 99:24–30
7. Babior BM: Oxygen-dependent microbial killing by phagocytes (first of two parts). N Engl J Med 1978; 298:659–68
8. Ratnaraj J, Kabon B, Talcott MR, Sessler DI, Kurz A: Supplemental oxygen and carbon dioxide each increase subcutaneous and intestinal intramural oxygenation. Anesth Analg 2004; 99:207–11
9. Greif R, Akça 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
10. Belda FJ, Aguilera L, García de la Asunción J, Alberti J, Vicente R, Ferrándiz L, Rodríguez R, Company R, Sessler DI, Aguilar G, Botello SG, Ortí R; Spanish Reduccion de la Tasa de Infeccion Quirurgica Group: Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. JAMA 2005; 294:2035–42
11. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Høgdall C, Lundvall L, Svendsen PE, Mollerup H, Lunn TH, Simonsen I, Martinsen KR, Pulawska T, Bundgaard L, Bugge L, Hansen EG, Riber C, Gocht-Jensen P, Walker LR, Bendtsen A, Johansson G, Skovgaard N, Heltø K, Poukinski A, Korshin A, Walli A, Bulut M, Carlsson PS, Rodt SA, Lundbech LB, Rask H, Buch N, Perdawid SK, Reza J, Jensen KV, Carlsen CG, Jensen FS, Rasmussen LS; PROXI

Trial Group: Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: The PROXI randomized clinical trial. JAMA 2009; 302:1543–50
12. Kurz A, Kopyeva T, Suliman I, Podolyak A, You J, Lewis B, Vlah C, Khatib R, Keebler A, Reigert R, Seuffert M, Muzie L, Drahuschak S, Gorgun E, Stocchi L, Turan A, Sessler DI: Supplemental oxygen and surgical-site infections: An alternating intervention controlled trial. Br J Anaesth 2018; 120:117–26
13. de Jonge S, Egger M, Latif A, Loke YK, Berenholtz S, Boermeester M, Allegranzi B, Solomkin J: 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
14. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS; PROXI Trial Group: Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: Follow-up of a randomized clinical trial. Anesth Analg 2012; 115:849–54
15. Hopf HW, Holm J: Hyperoxia and infection. Best Pract Res Clin Anaesthesiol 2008; 22:553–69
16. Qadan M, Battista C, Gardner SA, Anderson G, Akca O, Polk HC Jr: Oxygen and surgical site infection: A study of underlying immunologic mechanisms. Anesthesiology 2010; 113:369–77
17. Snyder GL, Greenberg S: Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 2010; 105:106–15
18. De Bels D, Corazza F, Germonpré P, Balestra C: The normobaric oxygen paradox: A novel way to administer oxygen as an adjuvant treatment for cancer? Med Hypotheses 2011; 76:467–70
19. Tertil M, Jozkowicz A, Dulak J: Oxidative stress in tumor angiogenesis- therapeutic targets. Curr Pharm Des 2010; 16:3877–94
20. Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS; PROXI Trial Group: Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. Br J Anaesth 2014; 113(suppl 1):i74–81
21. Podolyak A, Sessler DI, Reiterer C, Fleischmann E, Akça O, Mascha EJ, Greif R, Kurz A: Perioperative supplemental oxygen does not worsen long-term mortality of colorectal surgery patients. Anesth Analg 2016; 122:1907–11
22. Ruetzler K, Cohen B, Leung S, Mascha EJ, Knotzer J, Kurz A, Sessler DI, Turan A: Supplemental intraoperative oxygen does not promote acute kidney injury or cardiovascular complications after noncardiac surgery: Subanalysis of an alternating intervention trial. Anesth Analg 2020; 130:933–40
23. Cohen B, Ruetzler K, Kurz A, Leung S, Rivas E, Ezell J, Mao G, Sessler DI, Turan A: Intra-operative high inspired oxygen fraction does not increase the risk of postoperative respiratory complications: Alternating intervention clinical trial. Eur J Anaesthesiol 2019; 36:320–6
24. Cohen B, Ahuja S, Schacham YN, Chelnick D, Mao G, Ali-Sakr Esa W, Maheshwari K, Sessler DI, Turan A: Intraoperative hyperoxia foes not reduce postoperative pain: Subanalysis of an alternating cohort trial. Anesth Analg 2019; 128:1160–6
25. Huntington JT, Butterfield M, Fisher J, Torrent D, Bloomston M: The Social Security Death Index (SSDI) most accurately reflects true survival for older oncology patients. Am J Cancer Res 2013; 3:518–22

Appendix

Table A1. Sensitivity Analyses: Effect of 80% *versus* 30% Oxygen Supplement on Long-term Mortality Including Patients from All States (N = 5,167)

	N	Long-term Mortality (%)	Median Follow-up (yr) [25th, 75th Percentiles]	2-yr Survival % (95% CI)	5-yr Survival % (95% CI)	Hazard Ratio (95% CI)	*P* Value
All operations*							0.534
30% Oxygen	2,552	267 (10)	1.7 [0.4, 4.5]	92% (90–93%)	82% (80–84%)	Reference = 1	
80% Oxygen	2,615	257 (10)	1.6 [0.3, 4.5]	92% (91–93%)	83% (80–85%)	0.95 (0.80–1.13)	
Only the first operation per patient†							0.656
30% Oxygen	2,040	268 (13)	3.4 [0.8, 5.1]	92% (90–93%)	82% (80–84%)	Reference = 1	
80% Oxygen	2,048	256 (13)	3.4 [0.7, 5.1]	91% (90–93%)	83% (80–85%)	0.96 (0.81–1.14)	
Only the last operation per patient‡							0.548
30% Oxygen	2,011	267 (13)	3.3 [0.7, 4.9]	91% (90–92%)	81% (79–84%)	Reference = 1	
80% Oxygen	2,077	257 (12)	3.3 [0.5, 4.9]	91% (90–92%)	82% (79–84%)	0.95 (0.80–1.13)	

*Multivariable random-effects Cox proportional hazards regression adjusting for time-weighted average of intraoperative heart rate (*i.e.*, imbalanced with absolute standardized difference greater than 0.1) and incorporating cluster-specific random effects of multiple surgeries within patients. †Multivariable random-effects Cox proportional hazards regression adjusting for smoking status (*i.e.*, imbalanced with absolute standardized difference greater than 0.1). ‡Multivariable random-effects Cox proportional hazards regression adjusting for time-weighted average of intraoperative heart rate (*i.e.*, imbalanced with absolute standardized difference greater than 0.1).

Table A2. Baseline and Intraoperative Factors for the First Operation of Ohio Patients (N = 2,801)

Variables	80% Oxygen (N = 1, 410)	30% Oxygen (N = 1, 391)	Absolute Standardized Difference*
Age, yr	55 ± 17	55 ± 17	0.028
Gender, No. (%)			0.026
Female	728 (52)	736 (53)	
Male	682 (48)	655 (47)	
Race, No. (%)			0.064
White	1254 (89)	1208 (87)	
Black	133 (10)	155 (11)	
Other	23 (1)	28 (2)	
Body mass index, kg/m^2	27 [23, 31]	27 [23, 32]	0.030
Smoking status, No. (%)			0.153
Current smoker	197 (14)	128 (9)	
Ex-smoker	431 (31)	427 (30)	
Never smoker	782 (55)	836 (60)	
ASA physical status, No. (%)			0.040
I	6 (0)	7 (0)	
II	415 (30)	381 (27)	
III	859 (61)	870 (63)	
IV	128 (9)	133 (10)	
V	2 (0)	0 (0)	
Medical history, No. (%)			
Congestive heart failure	57 (4)	64 (5)	0.027
Vascular disease	57 (4)	64 (5)	0.027
Pulmonary circulation disease	69 (5)	52 (4)	0.057
Peripheral vascular disease	98 (7)	83 (6)	0.040
Hypertension, uncomplicated	507 (36)	490 (35)	0.015
Hypertension, complicated	62 (4)	66 (5)	0.017
Paralysis	15 (1)	15 (1)	0.001
Other neurologic disorders	61 (4)	81 (6)	0.068
Chronic pulmonary disease	216 (15)	204 (15)	0.018
Diabetes without chronic complications	145 (10)	136 (10)	0.017
Diabetes with chronic complications	33 (2)	46 (3)	0.058
Hypothyroidism	142 (10)	154 (11)	0.033
Renal failure	74 (5)	77 (6)	0.013
Liver disease	39 (3)	39 (3)	0.002
Peptic ulcer disease (bleeding)	2 (0)	1 (0)	0.021
AIDS	3 (0)	1 (0)	0.037
Lymphoma	29 (2)	29 (2)	0.002
Metastatic cancer	125 (9)	130 (9)	0.017
Solid tumour without metastasis	321 (23)	272 (20)	0.079
Rheumatoid arthritis/collagen vascular disease	60 (4)	65 (5)	0.020
Coagulopathy	114 (8)	90 (7)	0.062
Obesity	293 (21)	314 (23)	0.044
Weight loss	384 (27)	358 (26)	0.034
Fluid and electrolyte disorders	589 (42)	576 (41)	0.007
Chronic blood loss anaemia	39 (3)	37 (3)	0.007
Deficiency anaemias	308 (22)	337 (24)	0.057
Alcohol abuse	28 (2)	29 (2)	0.007
Drug abuse	38 (3)	34 (2)	0.016
Psychoses	80 (6)	69 (5)	0.032
Depression	245 (17)	232 (17)	0.019
Primary diagnosis, No. (%)			0.074
Cancer	676 (48)	642 (46)	
Crohn disease	233 (17)	227 (16)	
Diverticulitis	154 (11)	155 (11)	
Ostomy	71 (5)	73 (5)	
Fistula	98 (7)	113 (8)	
Hernia	24 (1)	30 (2)	
Other	154 (11)	151 (12)	
Preoperative oral antibiotic, No. (%)	773 (55)	765 (55)	0.003
Preoperative bowel preparation medication, No. (%)	363 (26)	327 (24)	0.052

(*Continued*)

Table A2. (*Continued*)

Variables	80% Oxygen (N = 1,410)	30% Oxygen (N = 1, 391)	Absolute Standardized Difference*
Type of surgery, No. (%)			0.093
Colorectal resection	892 (63)	841 (61)	
Lower gastrointestinal therapeutic procedures	295 (21)	304 (22)	
Small bowel resection	85 (6)	96 (7)	
Exploratory laparotomy	24 (2)	37 (2)	
Excision	22 (2)	21 (2)	
Laparoscopy	31 (2)	33 (2)	
Hernia repair	24 (2)	24 (2)	
Ileostomy and other enterostomy	17 (1)	20 (1)	
Colostomy	20 (1)	15 (1)	
Laparoscopic surgery (*vs.* open or converted), No. (%)	485 (34)	450 (32)	0.043
Duration of surgery, h	4.3 ± 1.7	4.4 ± 1.8	0.027
Regional block, No. (%)	29 (2)	40 (3)	0.053
Spinal or epidural anesthesia, No. (%)	112 (8)	125 (9)	0.037
Attending anesthesiologist,† No. (%)			—‡
A	182 (13)	180 (13)	
B	194 (14)	178 (13)	
C	48 (3)	77 (6)	
D	74 (5)	41 (3)	
E	32 (2)	43 (3)	
Operating room number, No. (%)			0.062
#47	323 (23)	308 (22)	
#48	317 (23)	299 (21)	
#50	261 (19)	266 (19)	
#46	194 (14)	191 (14)	
#45	191 (14)	201 (15)	
#49	68 (5)	79 (6)	
#40–44	56 (4)	47 (3)	
Intraoperative management			
Time-weighted average of esophageal temperature, °C	36.0 ± 0.6§	36.0 ± 0.6‖	0.077
Esophageal temperature at end of case, °C	36.4 [35.9, 36.8]§	36.4 [35.9, 36.8]‖	0.021
Time-weighted average of MAP, mmHg	87 ± 9	86 ± 9	0.112
Time-weighted average of HR, beats/min	76 ± 11	78 ± 12	0.094
Amount of anesthetic gas (MAC), h	3.1 [2.2, 4.2] #	3.1 [2.1, 4.3]**	0.030
Fraction of inspired oxygen, %	80 [78, 82]	39 [35, 48]	3.132
Time-weighted average of P_{ETCO_2}, mmHg	35 ± 2	35 ± 2	0.016
Time-weighted average of glucose, mg/dl	142 [122, 164]††	141 [120, 165]‡‡	0.041
Crystalloid volume, l	2.8 [2.1, 3.6]	2.9 [2.1, 3.7]	0.024
Laparoscopic surgery	2.8 [2.2, 3.4]	2.8 [2.2, 3.5]	
Open surgery	2.9 [2.0, 3.8]	2.9 [2.0, 3.8]	
Colloid volume, l	0 [0, 0.5]	0 [0, 0.5]	0.092
Estimated blood loss, ml	100 [50, 250]	100 [50, 250]	0.040
Blood transfusion, No. (%)	136 (10)	131 (9)	0.008
Amount of blood transfusion among patients who were transfused, l	0.7 [0.4, 1.0]	0.7 [0.4, 1.0]	0.005

Summary statistics (presented as % of patients, mean ± SD, or median [25th, 75th percentiles], respectively, for factors, symmetric continuous variables, and skewed continuous variables).

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD. Any baseline or procedural variables with an absolute standardized difference greater than 0.10 was considered to be imbalanced and would be adjusted for in the analysis. †Five attending anesthesiologists (of 64) with most cases are listed, due to the limited space. ‡Absolute standardized difference was not calculated due to too many categories (among 64 anesthesiologists). §A total of 57 cases have missing data. ‖A total of 45 cases have missing data. #One case has missing data. **Five cases have missing data. ††A total of 952 cases have missing data. ‡‡A total of 911 cases have missing data.

AIDS, acquired immune deficiency syndrome; ASA, American Society of Anesthesiologists; HR, heart rate; MAC, minimal alveolar concentration; MAP, mean arterial blood pressure; P_{ETCO_2}, end-tidal pressure of carbon dioxide.

Table A3. Baseline and Intraoperative Factors for the Last Operation of Ohio Patients (N = 2,801)

Variables	80% Oxygen (N = 1, 412)	30% Oxygen (N = 1, 389)	Absolute Standardized Difference*
Age, yr	56 ± 17	54 ± 17	0.073
Gender, No. (%)			0.003
Female	739 (52)	725 (52)	
Male	673 (48)	664 (48)	
Race, No. (%)			0.063
White	1255 (89)	1207 (87)	
Black	132 (9)	156 (11)	
Other	25 (2)	26 (2)	
Body mass index, kg/m^2	26 [23, 31]	27 [23, 31]	0.012
Smoking status, No. (%)			0.123
Current smoker	191 (14)	136 (10)	
Ex-smoker	431 (30)	418 (30)	
Never smoker	790 (56)	835 (60)	
ASA physical status, No. (%)			0.002
I	6 (1)	6 (1)	
II	399 (28)	392 (28)	
III	875 (62)	863 (62)	
IV	130 (9)	128 (9)	
V	2 (0)	0 (0)	
Medical history, No. (%)			
Congestive heart failure	67 (5)	57 (4)	0.031
Vascular disease	63 (5)	61 (4)	0.003
Pulmonary circulation disease	70 (5)	57 (4)	0.041
Peripheral vascular disease	102 (7)	91 (7)	0.027
Hypertension, uncomplicated	526 (37)	478 (34)	0.059
Hypertension, complicated	71 (5)	67 (5)	0.009
Paralysis	19 (1)	13 (1)	0.039
Other neurologic disorders	76 (5)	78 (6)	0.010
Chronic pulmonary disease	223 (16)	209 (15)	0.021
Diabetes without chronic complications	145 (10)	136 (10)	0.016
Diabetes with chronic complications	38 (3)	46 (3)	0.036
Hypothyroidism	146 (10)	154 (11)	0.024
Renal failure	80 (6)	80 (6)	0.004
Liver disease	40 (3)	40 (3)	0.003
Peptic ulcer disease (bleeding)	2 (0)	1 (0)	0.021
AIDS	3 (0)	1 (0)	0.037
Lymphoma	33 (2)	25 (2)	0.038
Metastatic cancer	124 (9)	137 (10)	0.037
Solid tumour without metastasis	326 (23)	269 (20)	0.091
Rheumatoid arthritis/collagen vascular disease	66 (5)	64 (5)	0.003
Coagulopathy	115 (8)	104 (8)	0.024
Obesity	296 (21)	334 (24)	0.074
Weight loss	405 (29)	395 (28)	0.005
Fluid and electrolyte disorders	635 (45)	628 (45)	0.005
Chronic blood loss anaemia	39 (3)	42 (3)	0.016
Deficiency anaemias	339 (24)	355 (26)	0.036
Alcohol abuse	30 (2)	31 (2)	0.007
Drug abuse	39 (3)	40 (3)	0.007
Psychoses	80 (6)	79 (6)	0.001
Depression	266 (19)	242 (17)	0.037
Primary diagnosis, No. (%)			0.065
Cancer	662 (47)	612 (44)	
Crohn disease	219 (16)	233 (17)	
Diverticulitis	147 (10)	145 (11)	
Ostomy	108 (7)	117 (8)	
Fistula	95 (7)	97 (7)	
Hernia	36 (3)	40 (3)	
Other	145 (10)	145 (10)	
Preoperative oral antibiotic, No. (%)	672 (48)	648 (47)	0.019
Preoperative bowel preparation medication, No. (%)	313 (22)	275 (20)	0.058

(*Continued*)

Table A3. (*Continued*)

Variables	80% Oxygen (N = 1, 412)	30% Oxygen (N = 1, 389)	Absolute Standardized Difference*
Type of surgery, No. (%)			0.096
Colorectal resection	753 (53)	709 (51)	
Lower gastrointestinal therapeutic procedures	426 (30)	433 (31)	
Small bowel resection	74 (5)	83 (6)	
Exploratory laparotomy	29 (2)	44 (3)	
Excision	27 (2)	21 (2)	
Laparoscopy	33 (2)	29 (2)	
Hernia repair	37 (3)	35 (3)	
Ileostomy and other enterostomy	18 (1)	22 (2)	
Colostomy	15 (1)	13 (1)	
Laparoscopic surgery (*vs.* open or converted), No. (%)	401 (28)	365 (26)	0.048
Duration of surgery, h	4.1 ± 1.7	4.1 ± 1.8	0.008
Regional block, No. (%)	33 (2)	43 (3)	0.047
Spinal or epidural anesthesia, No. (%)	106 (8)	109 (8)	0.013
Attending anesthesiologist,† No. (%)			—‡
A	191 (14)	179 (13)	
B	187 (13)	185 (13)	
C	61 (4)	83 (6)	
D	65 (5)	41 (3)	
E	28 (2)	43 (3)	
Operating room number, No. (%)			0.100
#47	310 (22)	283 (20)	
#48	290 (20)	263 (19)	
#50	250 (18)	271 (20)	
#46	216 (15)	215 (16)	
#45	210 (15)	217 (16)	
#49	73 (5)	91 (6)	
#40–44	63 (5)	49 (3)	
Intraoperative management			
Time-weighted average of esophageal temperature, °C	36.0 ± 0.6§	36.0 ± 0.6‖	0.054
Esophageal temperature at end of case, °C	36.4 [35.9, 36.8] §	36.3 [35.8, 36.8] ‖	0.010
Time-weighted average of MAP, mmHg	86 ± 9	85 ± 9	0.093
Time-weighted average of HR, beats/min	76 ± 11	77 ± 11	0.154
Amount of anesthetic gas (MAC), h	2.9 [2.0, 4.0] #	2.8 [1.9, 4.0] **	0.037
Fraction of inspired oxygen, %	80 [78, 82]	39 [35, 47]	3.095
Time-weighted average P_{ETCO_2}, mmHg	35 ± 2	35 ± 2	0.018
Time-weighted average of glucose, mg/dl	141 [121, 163]††	139 [117, 164]‡‡	0.060
Crystalloid volume, l	2.6 [1.9, 3.4]	2.6 [1.8, 3.5]	0.011
Laparoscopic surgery	2.7 [2.1, 3.3]	2.7 [2.1, 3.4]	
Open surgery	2.5 [1.7, 3.5]	2.6 [1.7, 3.5]	
Colloid volume, l	0 [0, 0.25]	0 [0, 0.5]	0.103
Estimated blood loss, ml	100 [50, 200]	100 [50, 200]	0.038
Blood transfusion, No. (%)	108 (7.6)	109 (7.8)	0.007
Amount of blood transfusion among patients who were transfused, l	0.6 [0.3, 1.0]	0.7 [0.4, 1.0]	0.009

Summary statistics (presented as % of patients, mean ± SD, or median [25th, 75th percentiles], respectively, for factors, symmetric continuous variables, and skewed continuous variables).

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD. Any baseline or procedural variables with an absolute standardized difference greater than 0.10 was considered to be imbalanced and would be adjusted for in the analysis. †Five attending anesthesiologists (of 64) with most cases are listed, due to the limited space. ‡Absolute standardized difference was not calculated due to too many categories (among 64 anesthesiologists). §A total of 64 cases have missing data. ‖A total of 51 cases have missing data. #One case has missing data. **Five cases have missing data. ††A total of 1,018 cases have missing data. ‡‡A total of 970 cases have missing data.

AIDS, acquired immune deficiency syndrome; ASA, American Society of Anesthesiologists; HR, heart rate; MAC, minimal alveolar concentration; MAP, mean arterial blood pressure; P_{ETCO_2}, end-tidal pressure of carbon dioxide.