Effect of High Perioperative Oxygen Fraction on Surgical Site Infection and Pulmonary Complications After Abdominal Surgery

The PROXI Randomized Clinical Trial

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See also p 1588 and Patient Page.

Context Use of 80% oxygen during surgery has been suggested to reduce the risk of surgical wound infections, but this effect has not been consistently identified. The effect of 80% oxygen on pulmonary complications has not been well defined.

Objective To assess whether use of 80% oxygen reduces the frequency of surgical site infection without increasing the frequency of pulmonary complications in patients undergoing abdominal surgery.

Design, Setting, and Patients The PROXI trial, a patient- and observer-blinded randomized clinical trial conducted in 14 Danish hospitals between October 2006 and October 2008 among 1400 patients undergoing acute or elective laparotomy.

Interventions Patients were randomly assigned to receive either 80% or 30% oxygen during and for 2 hours after surgery.

Main Outcome Measures Surgical site infection within 14 days, defined according to the Centers for Disease Control and Prevention. Secondary outcomes included atelectasis, pneumonia, respiratory failure, and mortality.

Results Surgical site infection occurred in 131 of 685 patients (19.1%) assigned to receive 80% oxygen vs 141 of 701 (20.1%) assigned to receive 30% oxygen (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.72-1.22; $P=.64$). Atelectasis occurred in 54 of 685 patients (7.9%) assigned to receive 80% oxygen vs 50 of 701 (7.1%) assigned to receive 30% oxygen (OR, 1.11; 95% CI, 0.75-1.66; $P=.60$), pneumonia in 41 (6.0%) vs 44 (6.3%) (OR, 0.95; 95% CI, 0.61-1.48; $P=.82$), respiratory failure in 38 (5.5%) vs 31 (4.4%) (OR, 1.27; 95% CI, 0.78-2.07; $P=.34$), and mortality within 30 days in 30 (4.4%) vs 20 (2.9%) (OR, 1.56; 95% CI, 0.88-2.77; $P=.13$).

Conclusion Administration of 80% oxygen compared with 30% oxygen did not result in a difference in risk of surgical site infection after abdominal surgery.

Trial Registration clinicaltrials.gov Identifier: NCT00364741

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SURGICAL SITE INFECTION IS A common and serious complication following abdominal surgery.[1] To prevent surgical site infection, it is essential to optimize perioperative conditions in the first hours following bacterial contamination.[2] Tissue oxygen tension is often low in wounds and colorectal anastomoses, and this may reduce tissue healing via oxidative killing by neutrophils and also reduce induction of collagen formation, neovascularization, and epithelialization.[3-7] Perioperative arterial and wound oxygen tension can be increased by a higher inspiratory oxygen fraction.[7]

Trials by Greif et al[8] and Belda et al[9] have suggested a significant reduction in the frequency of surgical wound in-

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fections when 80% rather than 30% oxygen was administered during surgery and in the first postoperative hours. Conversely, a trial by Mayzler et al[10] found no significant difference, a trial by Pryor et al[11] was stopped prematurely because the frequency of wound infection was more than doubled with high oxygen fraction, and a trial by Gardella et al[12] was stopped for futility. High inspiratory oxygen concentrations throughout the perioperative period also may result in pulmonary complications, but this important aspect has been studied in only 30 patients.[13] In a subgroup of patients from the trial by Greif et al,[8] there was a nonsignificant increase in the size of computed tomography (CT) scan–detected areas of atelectasis in the group receiving 80% oxygen.[13]

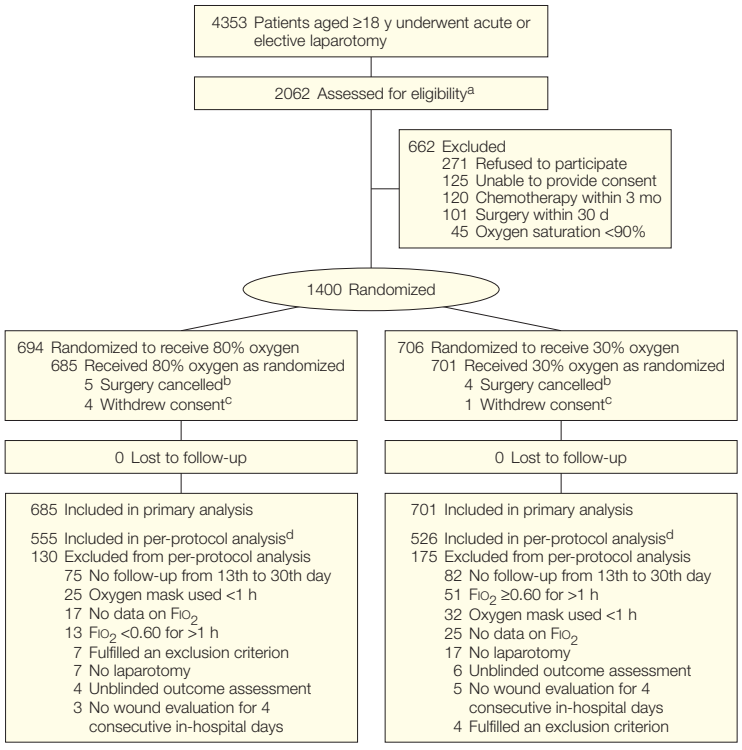
Furthermore, a high inspiratory oxygen fraction has been related to detrimental effects such as an increased risk of airway inflammation,[14] poor regulation of blood glucose levels,[15] and changes in the cardiac index[16] but has also been related to benefits such as improved healing of colorectal anastomosis[17] and reduced frequency of postoperative nausea and vomiting.[18,19]

The aim of this trial was to assess the benefits and harms of a high perioperative oxygen fraction in a general surgical population of patients undergoing laparotomy, the primary outcome measure being surgical site infection. We hypothesized that 80% oxygen would reduce the frequency of surgical site infections without increasing the frequency of pulmonary complications.

METHODS

The Danish Medicines Agency and the regional ethics committee approved the trial, which adhered to the International Conference on Harmonisation Good Clinical Practice standards. Written informed consent was obtained from all patients participating in this multicenter trial in 14 Danish hospitals between October 8, 2006, and October 6, 2008. Patients were eligible if they were 18 years or older and scheduled to undergo acute or elective laparotomy. When laparotomy was indicated for a gynecological disease, only patients with suspected malignancy (defined as risk of ovarian malignancy index >200 or a specimen showing atypical or neoplastic cells[20]) were included. Exclusion criteria were operations performed under general anesthesia within 30 days, chemotherapy for malignancy within 3 months, inability to provide informed consent, and preoperative arterial hemoglobin oxygen saturation below 90% without supplemental oxygen assessed by pulse oximetry.

Figure. Patient Enrollment, Randomization, and Treatment Flow



FIO_2 indicates inspiratory oxygen fraction.
[a] Underwent surgery when research staff were present.
[b] No outcome data described for these patients.
[c] No baseline or outcome data described for these patients.
[d] Patients could be excluded for more than 1 reason.

Trial Protocol

Patients were randomized according to a computer-generated allocation list by a central interactive voice-response system at the Copenhagen Trial Unit using study center, diabetes mellitus, acute or elective operations, and body mass index (<30 or ≥30, calculated as weight in kilograms divided by height in meters squared) as stratification variables.

The trial protocol[21] included several important aspects of perioperative care, including epidural analgesia, control of temperature and glucose level, absence of preoperative oral bowel preparation, and standardized anesthesia without nitrous oxide. The protocol recommended cefuroxime (1.5 g) and metronidazole (1 g) given intravenously as standard antibiotic choice, but ampicillin (2 g) or benzylpenicillin (2 million IU) in combination with gentamicin (0.240 g) and metronidazole (1 g) were also allowed.[21] Fewer antibiotics were required in the case of elective cholecystectomy or laparotomies with no potential contamination. We considered "timely" administration of antibi-

otics as administration of the first and second antibiotic within 60 minutes prior to skin incision. Perioperative fluids were given only to replace measured or calculated deficits (no third-space loss), aiming at a postoperative body weight increase of less than 1 kg. Blood loss was replaced 1:1 with colloids, and blood transfusion was initiated if blood loss exceeded 20 mL/kg.[21]

Anesthesia was either inhalational or total intravenous anesthesia, determined entirely by the attending anesthetist. An inspiratory oxygen fraction (FIO_2) of 1.0 was used at induction of anesthesia until tracheal intubation and again immediately before tracheal extubation. After induction of anesthesia and tracheal intubation, patients randomized to the 80% oxygen group were given an FIO_2 of 0.80 until the end of surgery. The first 2 hours following extubation, patients breathed an FIO_2 of 0.80 administered by means of a nonrebreathing face mask with a reservoir (High Concentration Oxygen Mask; Intersurgical Ltd, Wokingham, United Kingdom) and a flow of 14 L of oxygen and 2 L of air per minute. The patients randomized to the 30% oxygen group were given an FIO_2 of 0.30 after tracheal intubation and received a mixture of 2 L of oxygen and 14 L of air per minute through an identical nonrebreathing face mask after extubation.[21] The patients were ventilated to ensure normocapnia.[21]

In both groups, FIO_2 was increased if hypoxia was detected or suspected to ensure arterial oxygen saturation greater than 94% and arterial oxygen tension greater than 9 kPa. Positive end expiratory pressure was used at a level chosen by the attending anesthetist. Two hours after surgery, supplemental oxygen was administered only at the physician's discretion and according to clinical practice.

The risk of infection was assessed with the NNISS (National Nosocomial Infections Surveillance System) and the SENIC (Study on the Efficacy of Nosocomial Infection Control) scales.[22,23]

Cardboard shields were placed on the side of the anesthesia machine to keep the surgical team blinded to group allocation. In the postanesthesia care unit, opaque bags covered the flow meters. Information about perioperative FIO_2, arterial oxygen tension, and flow of oxygen and air was noted on a separate paper form and placed in a sealed opaque envelope in the medical record when patients were discharged from the postanesthesia care unit. The staff on the wards and the patients were not informed during follow-up about the intervention received.

To evaluate participant blinding, the patients were asked which of the groups they believed they belonged to and to give a reason for their choice. No investigator had access to patient allocation and outcome data at the same time. All statistical analyses were performed with the intervention groups named A and B, and the statistician was blinded to allocation. This manuscript, including the discussion and conclusion, was written in 2 versions, one based on the assumption that treatment A was 80% oxygen and treatment B was 30% oxygen and the other based on the reverse assumption.[21,24] All authors approved both versions before unmasking the allocation groups.[21]

The primary outcome was surgical site infection within 14 days of surgery, defined according to criteria from the Centers for Disease Control and Prevention (CDC) as superficial or deep wound infection or as intra-abdominal organ/space infection.[25] The secondary outcomes were pneumonia within 14 days (according to CDC criteria[26]), atelectasis within 14 days, respiratory failure within 14 days (defined as the need for controlled ventilation or arterial oxygen saturation below 90% despite supplemental oxygen), mortality within 30 days, duration of postoperative hospitalization, admission to the intensive care unit within 14 days (if not part of postoperative care), and abdominal reoperation for any reason within 14 days.

The patients were seen daily in the postoperative period by a surgical

Table 1. Characteristics of Patients Scheduled for Laparotomy (N = 1395)[a]

Characteristic	80% Oxygen (n = 690)	30% Oxygen (n = 705)
Age, median (5%-95%), y	64 (27-85)	64 (34-84)
Men, No. (%)	288 (41.7)	297 (42.1)
Height, median (5%-95%), cm	170 (156-185)	170 (154-186)
Weight, median (5%-95%), kg	71 (49-109)	72 (50-103)
Body mass index, median (5%-95%)[b]	25 (18-35)	25 (19-35)
Body mass index ≥30, No. (%)[b]	102 (14.8)	111 (15.7)
ASA physical status score, No. (%)		
1	176 (25.5)	199 (28.2)
2	378 (54.8)	376 (53.3)
3	132 (19.1)	125 (17.7)
4	4 (0.6)	5 (0.7)
Acute surgery	190 (27.5)	195 (27.7)
History, No. (%)		
Current smoker	207 (30.0)	213 (30.2)
Alcohol consumption >48 g/d	29 (4.2)	35 (5.0)
Previous abdominal surgery	298 (43.2)	310 (44.0)
Diabetes mellitus	51 (7.4)	53 (7.5)
Chronic obstructive pulmonary disease	35 (5.1)	34 (4.8)
Other pulmonary disease	45 (6.5)	48 (6.8)
Hypertension	209 (30.3)	187 (26.5)
Other cardiovascular disease	125 (18.1)	96 (13.6)
Current signs of infection	76 (11.0)	66 (9.4)
Immune deficiency	27 (3.9)	30 (4.3)
Other disease[c]	209 (30.3)	228 (32.3)
Preoperative risk score, No. (%)[d]		
SENIC		
1	232 (33.6)	228 (32.3)
2	345 (50.0)	362 (51.3)
3	99 (14.3)	102 (14.5)
4	14 (2.0)	13 (1.8)
NNISS		
0	297 (43.0)	309 (43.8)
1	275 (39.9)	292 (41.4)
2	106 (15.4)	93 (13.2)
3	12 (1.7)	11 (1.6)

Abbreviations: ASA, American Society of Anesthesiologists; NNISS, National Nosocomial Infection Surveillance System; SENIC, Study on the Efficacy of Nosocomial Infection Control.

[a] All participants except those who withdrew consent. All characteristics have less than 0.5% missing data.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] History of various conditions, predominantly neurologic and musculoskeletal disorders.

[d] Higher scores indicate higher risk of infection. In the SENIC scoring system,[22] 1 point is given for each of (1) presence of 3 or more diagnoses; (2) surgery lasting longer than 2 hours; (3) operation classified as contaminated or dirty-infected; (4) abdominal surgery. In the NNISS scoring system,[23] 1 point is given for (1) ASA score of 3, 4, or 5; (2) operation classified as contaminated or dirty-infected; (3) operation lasting longer than expected for the operative procedure being performed.

investigator blinded to allocation. A follow-up visit was conducted between the 13th and 30th postoperative day. Surgical site infection, pulmonary complications, and other adverse events were evaluated at each visit, and additional information about wound characteristics in the postoperative period were collected to calculate the ASEPSIS (additional treatment, serous exudate, erythema, purulent exudate, separation of deep tissues, isolation of bacteria, and duration of inpatient stay) score.[27]

Patients with symptoms of pulmonary complications were examined according to clinical practice by the attending physician, including chest radiographs or CTs when relevant. All chest radiographs and CTs were evaluated for infiltrate and atelectasis by the attending radiologist, who was unaware of the intervention applied. Atelectasis was considered present if described in the radiologist's evaluation of chest radiograph or CT. Adverse events were collected prospectively according to the CONSORT (Consolidated Standards of Reporting Trials) Statement[28] and specifically addressed at the follow-up visit.[21]

If patients did not attend the follow-up visit, we contacted hospital outpatient clinics, emergency departments, and the patient's family physician for information about outcome and adverse events. Wound evaluation carried out in accordance with the CDC criteria was considered adequate. The patients were interviewed by telephone in the remaining cases. The complete statistical analysis plan is described in the protocol.[21]

Patients were excluded from the per-protocol analysis if they did not meet the inclusion criteria, fulfilled an exclusion criterion, had an F_{IO_2} greater than 0.60 for more than 1 hour (30% oxygen group) or an F_{IO_2} less than 0.60 for more than 1 hour (80% oxygen group), used an oxygen mask less than 1 hour, had no in-hospital evaluation of the outcomes for 4 or more consecutive days, or had no follow-up visit between the 13th and 30th postoperative day; patients were also excluded if assessors were unblinded.

Table 2. Perioperative Characteristics of 1386 Patients Scheduled for Laparotomy[a]

Characteristic	80% Oxygen (n = 685)	30% Oxygen (n = 701)
Surgical procedure, No. (%)		
Colorectal procedures	303 (44.2)	330 (47.1)
Gynecological procedures	139 (20.3)	129 (18.4)
Small-bowel surgery	78 (11.4)	80 (11.4)
Appendectomy	61 (8.9)	63 (9.0)
Other[b]	104 (15.2)	99 (14.1)
Diagnosis, No. (%)		
Cancer	352 (51.4)	362 (51.6)
Benign neoplasm	63 (9.2)	45 (6.4)
Appendicitis	61 (8.9)	60 (8.6)
Intestinal obstruction due to benign disease	58 (8.5)	66 (9.4)
Inflammatory bowel disease	37 (5.4)	42 (6.0)
Diverticulitis	23 (3.4)	34 (4.9)
Other[c]	91 (13.3)	92 (13.1)
Preoperative hemoglobin, median (5%-95%), g/dL	13 (10 to 16)	13 (9 to 16)
Preoperative glucose, median (5%-95%), mg/dL (n = 605 vs 623)	110 (76 to 175)	112 (77 to 180)
Perioperative glucose change, median (5%-95%), mg/dL (n = 560 vs 564)	16 (–27 to 79)	14 (–40 to 83)
Duration of anesthesia, median (5%-95%), min	190 (75 to 395)	195 (75 to 371)
Duration of surgery, median (5%-95%), min	128 (38 to 310)	132 (35 to 295)
Dose of ephedrine, median (5%-95%), mg	15 (0 to 50)	10 (0 to 50)
Requiring other vasopressors, No. (%)	209 (30.5)	229 (32.7)
Epidural analgesia, No. (%)		
Thoracic	453 (66.1)	479 (68.3)
Lumbar	20 (2.9)	19 (2.7)
None	212 (30.9)	203 (29.0)
Type of anesthesia, No. (%)		
Inhalational	178 (26.0)	208 (29.7)
Total intravenous	507 (74.0)	493 (70.3)
Perioperative dexamethasone, No. (%)	225 (32.8)	215 (30.7)
Antibiotic prophylaxis, No. (%)[d]		
Cefuroxime	22 (3.2)	13 (1.9)
Cefuroxime, metronidazole, and/or gentamicin	436 (63.6)	447 (63.8)
Ampicillin/penicillin, metronidazole, and gentamicin	74 (10.8)	86 (12.3)
Other	115 (16.8)	112 (16.0)
None	38 (5.5)	43 (6.1)
Receiving adequate antibiotic prophylaxis, No. (%)	580 (84.7)	589 (84.0)
Receiving timely antibiotic prophylaxis, No. (%)[e]	432 (66.8)	448 (68.1)
Incision extending above the umbilicus, No. (%)	439 (64.1)	463 (66.0)
Abdominal closure, No. (%)		
Sutures	157 (22.9)	163 (23.3)
Staples	528 (77.1)	538 (76.7)
Operation classification, No. (%)		
Clean	172 (25.1)	146 (20.8)
Clean-contaminated	377 (55.0)	419 (59.8)
Contaminated	115 (16.8)	120 (17.1)
Dirty-infected	21 (3.1)	16 (2.3)
Temperature at end of surgery, median (5%-95%), °C (n = 637 vs 635)	36.1 (35.0 to 37.6)	36.1 (35.1 to 37.4)

(continued)

Statistical Analysis

The intervention effect was assessed both with and without adjustment for the stratification variables as well as for chronic obstructive pulmonary dis-

ease, daily smoking, and surgical incision extending above the umbilicus. All intervention-effect estimates were reported with 95% confidence intervals (CIs), and a 2-sided $P < .05$ was considered statistically significant. Analyses were performed using R version 2.8.0 (http://www.r-project.org).

In the protocol we estimated that the frequency of surgical site infection would be 16% in the 30% oxygen group.[21] This was based on the previously reported frequencies[8-11] and the inclusion of acute laparotomies in our trial. A meta-analysis with a fixed-effects model showed a relative risk reduction of 25% if all 4 completed trials are included and of 48% if all but the Pryor trial[11] are considered. We thus expected a relative risk reduction of 33%. We calculated that a total sample size of 1400 patients would allow us to detect or reject a difference in surgical site infection of between 11% and 16% with 5% type I error risk, 80% power, and 10% dropout. In accordance, we identified a lack of information of more than 1400 randomized patients in a trial sequential analysis[29] of the meta-analysis of all trials conducted prior to the PROXI trial to detect or reject a 33% relative risk reduction in a future meta-analysis.[21]

An independent data monitoring committee recommended continuing the trial after the interim analysis, based on 40% of the records, was performed on January 24, 2008.[21]

RESULTS

A total of 1400 patients were randomized and 1386 included in the modified intention-to-treat analysis (FIGURE). Fourteen patients were excluded because of withdrawn informed consent or cancellation of surgery after randomization. Demographic and perioperative characteristics were similar in the 2 groups (TABLE 1 and TABLE 2).

Surgical site infection occurred in 131 of 685 (19.1%) vs 141 of 701 (20.1%) patients in the 80% and 30% oxygen groups, respectively (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.72-1.22; $P = .64$) (TABLE 3). The incidence of pulmonary complications was not significantly different, with atelectasis occurring in 54 of 685 (7.9%) vs 50 of 701 (7.1%) patients (OR, 1.11; 95% CI, 0.75-1.66), pneumonia in 41 (6.0%) vs 44 (6.3%) (OR, 0.95; 95% CI, 0.61-1.48), and respiratory failure in 38 (5.5%) vs 31

Table 2. Perioperative Characteristics of 1386 Patients Scheduled for Laparotomy[a] (continued)

Characteristic	80% Oxygen (n = 685)	30% Oxygen (n = 701)
Peroperative fluid management, median (5%-95%), mL		
Estimated blood loss	260 (0 to 2120)	250 (0 to 1800)
Crystalloid infusion	1100 (300 to 3000)	1100 (300 to 3000)
Colloid infusion	500 (0 to 1750)	500 (0 to 1500)
Patients receiving blood, No. (%)	121 (17.7)	121 (17.3)
Units transfused per patient, median (5%-95%)	2 (1 to 6)	2 (1 to 6)
Perioperative body weight change, median (5%-95%), kg[f]	0.9 (–4.5 to 5.4)	1.3 (–3.1 to 5.0)

SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.
[a] All characteristics have less than 0.5% missing data unless otherwise stated.
[b] Includes cholecystectomy, repair of hernia, gastric and hepatobiliary resections, nephrectomy, and splenectomy.
[c] Includes perforated peptic ulcer and cholecytolithiasis.
[d] Minimum antibiotic doses: Cefuroxime 1.5 g, metronidazole 1 g, gentamicin 0.240 g, ampicillin 2 g, or benzylpenicillin 2 million IU. Ceftriaxone 2.0 g was considered equivalent to cefuroxime 1.5 g in 72 patients, and dicloxacillin 2.0 g considered equivalent to benzylpenicillin 2 million IU in 9 patients.
[e] Administration of antibiotics was considered timely if the first and second antibiotic were given before skin incision. Percentages are among patients receiving antibiotic prophylaxis.
[f] Calculated for 299 vs 302 patients in whom body weight was measured preoperatively as well as on the first or second postoperative day.

Table 3. Clinical Outcomes for Patients Scheduled for Laparotomy (N = 1386)

Outcome	No. (%) 80% Oxygen (n = 685)	No. (%) 30% Oxygen (n = 701)	Univariate OR (95% CI)	P Value	Adjusted OR (95% CI)[a]	P Value
Surgical site infection	131 (19.1)	141 (20.1)	0.94 (0.72 to 1.22)	.64	0.91 (0.69 to 1.20)	.51
Infection location						
Superficial	75 (57.3)	76 (53.9)				
Deep	20 (15.3)	26 (18.4)				
Organ/space	36 (27.5)	39 (27.7)				
ASEPSIS score >20[b]	32 (4.7)	36 (5.1)				
Atelectasis	54 (7.9)	50 (7.1)	1.11 (0.75 to 1.66)	.60	1.13 (0.75 to 1.72)	.56
Pneumonia	41 (6.0)	44 (6.3)	0.95 (0.61 to 1.48)	.82	0.95 (0.60 to 1.49)	.81
Health care–associated	30 (73.2)	30 (68.2)				
Ventilator-associated	7 (17.1)	9 (20.5)				
Aspiration	2 (4.9)	1 (2.3)				
Community-acquired	2 (4.9)	2 (4.5)				
Immunocompromised	0	2 (4.5)				
Respiratory failure	38 (5.5)	31 (4.4)	1.27 (0.78 to 2.07)	.34	1.22 (0.74 to 2.03)	.44
Reoperation	104 (15.2)	104 (14.8)	1.03 (0.77 to 1.38)	.86	1.01 (0.75 to 1.37)	.93
Admission to ICU[c]	50 (7.3)	44 (6.3)	1.18 (0.77 to 1.79)	.45	1.21 (0.78 to 1.89)	.40
30-d mortality	30 (4.4)	20 (2.9)	1.56 (0.88 to 2.77)	.13	1.55 (0.86 to 2.85)	.15
Postoperative hospitalization, d	6 (1-34)	7 (2-36)	–0.69 (–2.3 to 0.93)	.09[d]		

Abbreviations: ASEPSIS, additional treatment, serous discharge, erythema, purulent exudate, separation of deep tissues, isolation of bacteria, and duration of postoperative stay; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.
[a] Adjusted for study center, body mass index (<30 or ≥30, calculated as weight in kilograms divided by height in meters squared), diabetes mellitus, acute or elective surgery, chronic obstructive pulmonary disease, current smoker, incision extending above the umbilicus, duration of surgery, and age (≥ 40 years or <40 years).
[b] Range of possible scores, 0-70. Combines wound appearance the first 5 postoperative days with additional surgical treatment; a score higher than 20 indicates wound infection.[27]
[c] Admissions to ICU excluded if part of routine postoperative care and lasting less than 24 hours (13 vs 9 patients in the 80% oxygen and 30% oxygen groups, respectively).
[d] Calculated with Wilcoxon unpaired rank sum test.

Table 4. Adverse Events Other Than Primary and Secondary Outcomes for Patients Scheduled for Laparotomy (N = 1386)

Adverse Event	No. (%) 80% Oxygen (n = 685)	No. (%) 30% Oxygen (n = 701)
Any	361 (52.7)	369 (52.6)
Wound-related	61 (8.9)	77 (11.0)
Infection		
Urinary tract	23 (3.4)	34 (4.9)
Other	79 (11.5)	83 (11.8)
Postoperative nausea or vomiting	136 (19.9)	135 (19.3)
Respiratory	63 (9.2)	57 (8.1)
Circulatory	57 (8.3)	67 (9.6)
Gastrointestinal tract	61 (8.9)	62 (8.8)
Other	150 (21.9)	152 (21.7)
Any serious adverse event	165 (24.1)	154 (22.0)
Sepsis	21 (3.1)	15 (2.1)
Other infection	29 (4.2)	34 (4.9)
Respiratory	27 (3.9)	25 (3.6)
Circulatory	24 (3.5)	20 (2.9)
Gastrointestinal tract	53 (7.7)	46 (6.5)
Other	47 (6.9)	44 (6.3)

(4.4%) (OR, 1.27; 95% CI, 0.78-2.07) in the 80% and 30% oxygen groups, respectively. Thirty patients (4.4%) died in the 30-day follow-up period in the 80% oxygen group, vs 20 patients (2.9%) in the 30% oxygen group (OR, 1.56; 95% CI, 0.88-2.77; $P=.13$).

Rupture of the abdominal fascia occurred in 23 of 685 (3.6%) vs 17 of 701 (2.4%) patients in the 2 groups. Among patients undergoing colorectal surgery, surgical site infection occurred in 72 of 303 (23.7%) vs 83 of 330 (25.2%) patients ($P=.68$) and mortality within 30 days in 14 of 303 (4.6%) vs 5 of 330 (1.5%) patients in the 80% and 30% oxygen groups, respectively ($P=.03$). Anastomotic leak occurred in 0 of 53 vs 2 of 49 (4.1%) after small bowel resections, 10 of 175 (5.7%) vs 10 of 174 (5.7%) after colonic resections, and 2 of 42 (4.8%) vs 6 of 49 (12.2%) after rectal resections in the 80% and 30% oxygen groups, respectively. Other adverse events are reported in TABLE 4.

One thousand eighty-one patients were included in the per-protocol analysis (Figure). Surgical site infection occurred in 122 of 555 (22.0%) vs 116 of 526 (22.1%) patients in the 80% and 30% oxygen groups, respectively ($P=.98$), and there were no significant differences regarding pulmonary complications.

When patients in the 80% oxygen group were asked about suspected treatment allocation, 16% of the patients reported assuming that they had received 80% oxygen and 5% that they had received 30% oxygen; 79% answered "do not know." The corresponding values for the 30% oxygen group were 15%, 5%, and 80%. Less than 1% of the reasons provided suggested unblinding.

COMMENT

Our trial did not find a 33% relative risk reduction in the frequency of surgical site infection when a high inspiratory oxygen fraction of 80% vs 30% was given in the perioperative period of acute or elective laparotomy. The high oxygen fraction was not associated with a significant increase in the frequency of pulmonary complications or other adverse events. Mortality differences were not statistically significant.

The primary strength of this trial is the inclusion of a large number of patients at risk of surgical site infection undergoing a wide range of laparotomies, including 28% acute procedures. Surgical site infection was defined according to the CDC criteria,[25] allowing for comparison with other trials. Follow-up was thorough, with assessment of all adverse events and vital status in all patients.

Our trial has some limitations. First, we were unable to apply the elements of the intended optimized regimen, such as timely administration of adequate antibiotics and prevention of hypothermia, to all patients. However, the distribution of the quality measures was similar in our 2 groups. Second, 51 of 701 patients (7.3%) in the 30% oxygen group required an F_{IO_2} of 0.60 or greater for more than 1 hour to maintain arterial oxygen saturation above 94%, in accordance with safety measures in clinical practice. Third, a total of 157 of 1386 patients (11.3%) did not have a follow-up visit between the 13th and 30th postoperative day, and some minor wound infections could thus have been missed during that period. However, follow-up status was obtained in all patients, because we reviewed all hospital admissions and visits to primary physicians when follow-up occurred beyond the 30th postoperative day. Our per-protocol analysis, in which we excluded these patients, showed a result similar to the intention-to-treat analysis. Fourth, the inclusion of different surgical procedures may be associated with the risk of overlooking a beneficial effect related to specific surgical procedures, such as colorectal resections. However, the effect on surgical site infection was similar in this subgroup, and in clinical practice the type of surgery is not always known at the time the F_{IO_2} is selected.

Two trials have suggested that high (80%) F_{IO_2} is effective in preventing surgical wound infections, with relative risk ratios of 39%[9] and 54%.[8] In contrast, 3 other trials did not report a significant reduction; one trial was stopped early because the frequency of surgical wound infections doubled,[11] one was statistically insignificant,[10] and recently, a large trial investigating a high oxygen fraction delivered via nonrebreathing face mask to prevent postcesarean surgical site infection was stopped for futility.[12] The relative risk reduction in our trial was only 5% in favor of the 80% oxygen group. Some important differences exist between our trial and the 2 trials showing benefit of high F_{IO_2},[8,9] because, according to current recommendations,[21] the patients in our trial received epidural analgesia, did not receive oral bowel preparation, and were not aggressively hydrated; however, they may have received more vasopressors during anesthesia.

The risk of surgical site infection, as evaluated by the level of the NNISS and SENIC scores, was similar to that in the previous trials,[8,9,11] although there were fewer medium-risk and more low-risk and high-risk patients

in our trial. This was related to the inclusion of gynecological and emergency procedures.

We found a frequency of surgical site infections comparable to that in the trial by Belda et al,[9] which also adhered to the CDC definition, but our event rate was higher than those previously reported.[8,10,11] These 3 trials, however, did not report the frequency of intra-abdominal organ/space surgical site infection. With an event rate of 19%, we had nearly 80% power to detect a 20% relative risk reduction. On the other hand, this trial has only 15% power to detect a 10% relative risk reduction, so we cannot exclude that a high perioperative oxygen fraction has a minor effect on surgical site infection.

Other additional trials have suggested that increased perioperative oxygen supply results in fewer wound infections. Patients undergoing nitrous oxide–free anesthesia with 80% oxygen had fewer wound infections than patients receiving nitrous oxide–based (30% oxygen, 70% nitrous oxide) anesthesia.[30] It is unclear whether nitrous oxide or the higher oxygen concentration caused this difference.[31] In a meta-analysis of 5 trials based on 3001 patients, including the nitrous oxide trial,[30] Qadan et al found that perioperative administration of 80% oxygen was associated with a reduced risk of surgical site infections.[32] However, when the data from our large trial are added to this existing evidence, it seems likely that the overall benefit of 80% oxygen observed by Qadan et al will be attenuated and perhaps even no longer statistically significant. Another large trial investigating the treatment of hypoxia via continuous positive airway pressure in the postoperative period also demonstrated a reduction in wound infections.[33]

Ventilation for only 5 minutes with 100% oxygen results in significantly larger areas of atelectasis than ventilation with lower oxygen concentrations,[34] and atelectasis on CT tended to be more frequent in patients receiving 80% oxygen compared with patients receiving 30% oxygen (94% vs 64%, $P=.12$) in a subgroup[13] of the trial by Greif et al.[8] We could not demonstrate significantly increased frequencies of pulmonary complications when 80% oxygen was given for a median of approximately 5 ½ hours. Our method of detecting atelectasis is likely to have resulted in fewer events than if a chest radiograph or CT was obtained routinely in all patients. On the other hand, we consider the reporting of asymptomatic atelectases to have less clinical relevance, and the frequency of atelectasis in our trial (7.5%) was the same as in the nitrous oxide–free group in the trial by Myles et al.[30] In the nitrous oxide–free group, the frequency of pneumonia (1.5%) was lower than in our trial (6.5%), which is more comparable to that reported by Squadrone et al,[33] in which 5.7% of patients with postoperative hypoxemia developed pneumonia. The difference may be caused by our thorough postoperative follow-up, because pneumonia was diagnosed within a median of 5 days after surgery.

The proportion of patients with respiratory failure and death within 30 days was higher in the 80% oxygen group; although those differences were not statistically different, these events were uncommon and the study did not have adequate power to assess this outcome. This finding is in contrast to previous trials comparing 80% and 30% oxygen.[8-11] The unadjusted OR for mortality in our trial was 1.56 (95% CI, 0.88-2.77) in favor of the 30% oxygen group. Thus, there was no evidence of a benefit in reducing mortality with a high perioperative F_{IO_2} (80%), although we recognize that a lack of important information must be addressed before this can be established beyond reasonable doubt, because our trial was not powered to document lethality differences.

Gynecological cancer surgery and acute laparotomies were included in this trial, but conversions of laparoscopic procedures to laparotomy were not eligible. Apart from conversion of laparoscopy, we believe the results of this trial may be generalizable to a general surgical population undergoing laparotomy.

In conclusion, administration of 80% oxygen compared with 30% oxygen during and for 2 hours after abdominal surgery did not result in a difference in risk of surgical site infection. The frequencies of pulmonary complications and mortality were not significantly different.

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