Inspiratory Oxygen Fraction and Postoperative Complications in Obese Patients

A Subgroup Analysis of the PROXI Trial

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ABSTRACT

Background: Obese patients are at a high risk of postoperative complication, including surgical site infection (SSI). Our aim was to evaluate the effect of a high inspiratory oxygen fraction (80%) on SSI and pulmonary complications in obese patients undergoing laparotomy.

Methods: This study was a planned analysis of the obese patients (body mass index ≥ 30 kg/m^2) recruited in the Danish multicenter, patient- and observer-blinded, PROXI Trial of 1,400 patients undergoing acute or elective laparotomy. Patients were randomized to receive either 80% or 30% oxygen during and for 2 h after surgery. The primary outcome was SSI within 14 days. Secondary outcomes were atelectasis, pneumonia, and respiratory failure.

Results: Two hundred thirteen patients had a body mass index ≥ 30 kg/m^2. The median (5–95% range) body mass index was 34 kg/m^2 (30–44) and 33 kg/m^2 (30–41) in patients allocated to the 80% and 30% oxygen group. SSI occurred in 32 of 102 (31%) *versus* 29 of 111 (26%) patients given 80% and 30% oxygen, respectively (odds ratio, 1.29; 95% CI, 0.71–2.34; $P = 0.40$). In addition, the incidence of pulmonary complications was not significantly different, with atelectasis occurring in 9% *versus* 6%, pneumonia in 6% *versus* 5%, and respiratory failure in 8% *versus* 5% in patients given 80% and 30% oxygen, respectively.

Conclusion: Administration of 80% oxygen, compared with 30% oxygen, did not reduce the frequency of SSI in obese patients. Moreover, no significant association was found between oxygen fraction and the risk of pulmonary complications.

What We Already Know about This Topic

- In the Danish multicenter PROXI Trial involving 1,400 patients, no significant reduction in surgical site infection was observed when 80% oxygen was given during and 2 h after abdominal surgery compared with use of 30% oxygen in all patients, although obese patients may be at high risk

What This Article Tells Us That Is New

- In this planned analysis of the obese subgroup (body mass index ≥ 30 kg/m^2, n = 231) of the PROXI Trial, there was no significant difference in the frequency of surgical site infection or postoperative pulmonary complications

OBESITY is associated with a high risk of postoperative complications, including atelectasis,[1] pneumonia,[2] thromboembolic events, cardiac complications, wound hernia, anastomotic leak, and surgical site infection (SSI).[3] The risk of complications is increased further in obese patients with modified metabolic syndrome.[4]

Arterial oxygenation and subcutaneous perfusion have an important role in the host defense against infection.[5] The bactericidal activity of neutrophils is mediated by oxidative killing,[6] which is dependent on the partial pressure of oxygen in the tissue. Subcutaneous oxygen tension (Psq_{O_2}) is often low during surgery, and this is significantly related to the development of SSI.[7] Psq_{O_2} can be increased with a high inspiratory oxygen fraction (F_{IO_2}), and two trials have found significant reduction in SSI when patients are given 80% compared with 30% oxygen

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during the perioperative period.[8,9] However, the PROXI Trial, involving 1,400 patients, recently showed no significant reduction in the frequency of SSI.[10]

The arterial oxygen tension is reduced more in obese than in lean patients during general anesthesia as a consequence of atelectasis and increased shunt fraction.[1,11] Moreover, obesity increases the size of individual fat cells without increasing blood flow,[12] resulting in subnormal total blood flow in relation to body weight[13] and relatively hypoperfused fat tissue,[11] but cardiac output, circulating blood volume, and resting oxygen consumption are increased.[14] This contributes to a more pronounced reduction of Psq_{O_2} in obese patients,[11] increased risk of SSI,[3] and thus a potential for enhanced effect of a high F_{IO_2}.

The aim of this planned subgroup analysis was to evaluate the effect of a high perioperative F_{IO_2} (80%) compared with 30% in obese patients undergoing laparotomy. We hypothesized that 80% oxygen would reduce the frequency of SSI. We also assessed the association between perioperative F_{IO_2} and the frequency of pulmonary complications and other complications.

Materials and Methods

The study was a planned subgroup analysis of the Danish multicenter PROXI Trial[15] and was approved by The Danish Medicines Agency and the regional ethics committee (NCT00364741, De Videnskabsetiske Komiteer for Region Hovedstaden, Hillerød, Denmark).[16] Written informed consent was obtained from all patients, and they were included between October 8, 2006, and October 6, 2008.

Eligible patients were 18 yr or older, had a preoperative body mass index (BMI) $\geq$ 30 kg/m^2, and were scheduled for acute or elective laparotomy.[15] Exclusion criteria were inability to give informed consent, chemotherapy for malignancy within 3 months, surgery performed under general anesthesia within 30 days, and preoperative arterial oxygen saturation less than 90% without supplemental oxygen as assessed by pulse oximetry.

Patients were randomized by a central interactive voice-response system at the Copenhagen Trial Unit to an F_{IO_2} of either 0.80 (the 80% oxygen group) or 0.30 (the 30% oxygen group) using the following stratification variables: study center, diabetes mellitus, and acute or elective surgery.

The trial protocol[15] emphasized an optimal perioperative care, including epidural analgesia, adequate temperature and glucose control, appropriate and timely prophylactic antibiotics, absence of preoperative oral bowel preparation, and standardized anesthesia without nitrous oxide. Perioperative fluids were given only to replace measured or calculated deficits aiming at 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.[15]

Patients were preoxygenated with an F_{IO_2} of 1.0 until tracheal intubation, after which patients were given the allocated F_{IO_2} until the end of surgery, when an F_{IO_2} of 1.0 was given immediately before extubation. The patients were ventilated to assure normocapnia.[15] In both groups, F_{IO_2} was increased to ensure arterial oxygen saturation above 94% and arterial oxygen tension above 9 kPa (68 mmHg). Positive end expiratory pressure was used at a level chosen by the attending anesthetist. Alveolar recruitment maneuvers were not routinely used but were allowed if the attending anesthetist thought they were clinically indicated.

The first 2 h after surgery, patients randomized to the 80% oxygen group breathed a F_{IO_2} of 0.80 *via* a nonrebreathing facemask with a reservoir (High Concentration Oxygen Mask, Intersurgical Ltd., Wokingham, United Kingdom) and an oxygen flow of 14 l/min and air flow of 2 l/min. The patients randomized to the 30% oxygen group received a mixture of oxygen (2 l/min) and air (14 l/min) through an identical nonrebreathing facemask.[15] Two hours after surgery, supplemental oxygen was administrated according to clinical practice.

The primary outcome was SSI within 14 days of surgery, defined according to the criteria by Centers for Disease Control and Prevention as superficial or deep wound infection or intraabdominal organ/space infection.[17] The secondary outcomes were atelectasis within 14 days, pneumonia within 14 days (according to the criteria by Centers for Disease Control and Prevention),§ and respiratory failure within 14 days (defined as the need for controlled ventilation or arterial oxygen saturation less than 90% despite supplemental oxygen). Tertiary outcomes were localization of SSI, admission to the intensive care unit within 14 days (if not part of routine postoperative care), another abdominal operation for any reason within 14 days, duration of postoperative hospitalization, wound-related adverse events, any adverse event, any serious adverse event, and mortality within 30 days.

The surgical investigator assessed all outcomes daily in the postoperative period, and a follow-up visit was conducted between postoperative days 13 and 30. The attending physician examined patients with symptoms of pulmonary complications according to clinical practice, including chest radiographs or computed tomography, when relevant. All chests radiographs and computed tomography were evaluated for infiltrate and atelectasis by the attending radiologist, who was blinded to allocation. The group allocation was also blinded to patients, outcome assessors, statisticians, the surgical team, and staff on the wards.[15]

Patients with the following major protocol deviations were not included in the per-protocol analysis[16]: did not meet the inclusion criteria, fulfilled an exclusion criterion, F_{IO_2} above 0.60 for more than 1 h in the 30% group, F_{IO_2} less than 0.60 for more than 1 h in the 80% oxygen group, oxygen mask used less than 1 h, no in-hospital evaluation of the outcomes for 4 consecutive days or more, no follow-up visit between postoperative days 13 and 30, and unblinding of outcome assessors.

§ Available at: http://www.cdc.gov/ncidod/hip/NNIS/members/pneumonia/Final/PneumoCriteriaV1.pdf. Accessed January 8, 2009.

Statistical Analysis

The complete statistical analysis plan is described in the trial protocol.[15] A univariate analysis was carried out for the primary and secondary outcomes and in a multivariate analysis, and the intervention effect was assessed after adjustment for the stratification variables as well as the design variables: chronic obstructive pulmonary disease, daily smoking, and surgical incision extending above the umbilical transversal. The tertiary outcomes were reported without statistical analyses. All intervention effect estimates were reported with 95% confidence limits and a two-sided P value of <0.05 was considered to indicate statistical significance. Analyses were performed using R version 2.8.0.‖

We estimated that the frequency of SSI would be 30% among obese patients,[3] and the frequency of obesity would be 20% among all patients included in the PROXI Trial, for which a total sample size of 1,400 patients was required.[15] We expected a high F_{IO_2} to be associated with a relative risk reduction of 50% in SSI in obese patients and calculated that we would have 80% power to detect this in our subgroup analysis with a 5% risk of type 1 error and 10% dropout.

Results

A total of 213 patients had a BMI $\geq$ 30 kg/m^2 (fig. 1). Demographic and perioperative characteristics were similar in the two groups (table 1).[18,19] The median (5–95% range) BMI was 34 kg/m^2 (30–44) and 33 kg/m^2 (30–41) in patients allocated to the 80% and 30% oxygen groups, respectively.

Surgical site infection occurred in 32 of 102 (31%) *versus* 29 of 111 (26%) patients in the 80% and the 30% oxygen groups, respectively (P = 0.40, table 2). The difference between the 80% and 30% oxygen groups in SSI was 5% (95% CI, 7–17%); in atelectasis, the difference was 3% (95% CI, −5 to 10%); in pneumonia, 1% (95% CI, −5 to 7%); and in respiratory failure, 3% (95% CI, −3 to 10%).

The incidence of SSI was 27% in obese patients (BMI = 30.0–34.9 kg/m^2) and 32% in morbidly obese patients (BMI $\geq$ 35.0 kg/m^2, fig. 2). Atelectasis occurred in 9% *versus* 5%, pneumonia in 6% *versus* 3%, and respiratory failure in 6% *versus* 5% in the obese and morbidly obese patients, respectively.

Overall, 52% of the patients experienced adverse events in the follow-up period (table 3). Approximately 21% of patients had serious complications, with sepsis occurring in 3%; 30-day mortality was 2%. The median duration of postoperative hospitalization was 6 *versus* 5 days in the 80% and 30% oxygen groups, respectively (table 3). Anastomotic leak occurred in 2 of 31 (6%) *versus* 2 of 41 (5%) patients, and rupture of the abdominal fascia occurred in 9 of 102 (9%) *versus* 6 of 111 (5%) patients in the 80% and the 30% oxygen groups, respectively. Forty-three (20%) patients underwent abdominal reoperation. Twenty-four (11%) patients underwent second operation because of SSI, including five (2%) debridement procedures. Fifteen (7%) patients had rupture of the abdominal fascia, compared with 9 of 658 (1%) of patients of normal weight in the PROXI Trial.

‖ Available at: http://www.r-project.org. Accessed January 30, 2011.

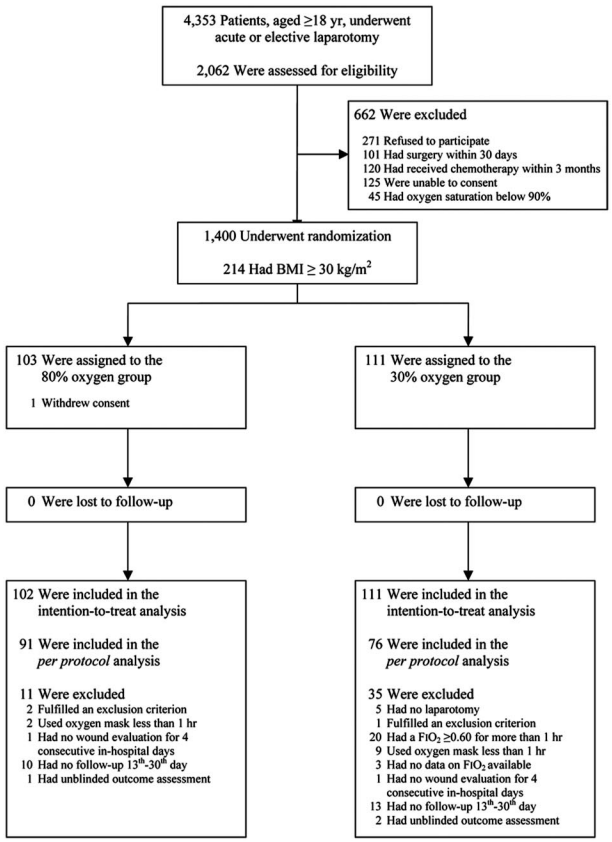

Fig. 1. Flowchart of patients scheduled for laparotomy. Each patient may have more than one reason for exclusion from the per protocol analysis. BMI = body mass index; F_{IO_2} = inspiratory oxygen fraction.

The per-protocol analysis (n = 167, fig. 1) of the primary and secondary outcomes showed a result similar to that of the intention-to-treat analysis, with SSI occurring in 31 of 91 (34%) *versus* 24 of 76 (32%) patients in the 80% and the 30% oxygen groups, respectively (P = 0.73).

Discussion

Contrary to our hypothesis, we did not find a reduction in the frequency of SSI in obese patients undergoing abdominal surgery when a high perioperative F_{IO_2} of 80% was given compared with when F_{IO_2} of 30% was given. The high perioperative F_{IO_2} was not associated with a significant increase in the frequency of pulmonary complication or other adverse events. In contrast, the primary and secondary outcomes all tended to be more common in patients allocated to 80% oxygen, but the power for the secondary outcomes was relatively low, as reflected in the wide confidence intervals. Therefore, we cannot exclude that a clinically important difference exists, but the detection of a difference in the incidence of respiratory failure between 4.5% and 8% would require a sample of nearly 2,000 patients with 80% power.

Table 1. Characteristics of 213 Obese Patients Scheduled for Laparotomy

	80% Oxygen Group (n = 102)	30% Oxygen Group (n = 111)
Age, yr	63 [37–81]	62 [35–78]
Sex, male/female	43/59	43/68
Preoperative weight, kg	96 [77–130]	96 [77–129]
BMI, kg/m^2	34 [30–44]	33 [30–41]
BMI ≥ 35.0 kg/m^2	39 (38%)	34 (31%)
ASA status, I/II/III	19/64/19	19/63/29
History		
Current smoker	31 (30%)	23 (21%)
Diabetes mellitus	16 (16%)	23 (21%)
Pulmonary disease	16 (16%)	11 (10%)
Hypertension	48 (47%)	53 (48%)
Other cardiovascular disease	15 (15%)	15 (14%)
Other disease*	41 (40%)	56 (50%)
Acute surgery	19 (19%)	20 (18%)
Preoperative risk score†		
SENIC, 1/2/3/4	24/32/42/4	25/35/47/4
NNISS, 0/1/2/3	20/50/26/6	28/47/29/7
Surgical procedure		
Colorectal procedures	40 (39%)	49 (44%)
Other surgery	62 (61%)	62 (56%)
Primary anastomotic procedures	31 (30%)	41 (37%)
Diagnosis		
Cancer	56 (55%)	57 (51%)
Other	46 (45%)	54 (49%)
Duration of surgery, min	145 [45–309]	135 [45–304]
Epidural analgesia		
Thoracic/lumbar/none	66/4/32	74/4/33
Type of anesthesia		
Volatile anesthesia	25 (25%)	41 (37%)
Total intravenous anesthesia	77 (75%)	70 (63%)
Timely antibiotic prophylaxis‡	64 (63%)	75 (71%)
Adequate antibiotic prophylaxis§	90 (88%)	91 (82%)
Operation classification		—
Clean	36 (35%)	35 (32%)
Clean-contaminated	21 (21%)	19 (17%)
Contaminated	43 (42%)	54 (49%)
Dirty-infected	2 (2.0%)	3 (2.7%)
Estimated blood loss, ml	418 [1–2074]	290 [0–2,000]
Weight change, kg‖	1 [−5 to 6]	1 [−5 to 6]

Values are N (%) or median [5–95% range].

* History of various conditions, predominantly musculoskeletal, infectious, and neurologic disorders. † Higher scores indicate higher risk of infection. In the SENIC scoring system, 1 point is given for each of the following: presence of 3 or more diagnoses; surgery lasting longer than 2 h; operation classified as contaminated or dirty-infected; and abdominal surgery. In the NNISS scoring system, 1 point is given for: ASA score of 3, 4, or 5; operation classified as contaminated or dirty-infected; and operation lasting longer than expected for the operative procedure being performed. ‡ Administration of antibiotics was considered timely if the first and second antibiotic were given within 60 min before skin incision. § Percentages are among patients receiving antibiotic prophylaxis. ‖ Calculated for 46 patients in each group in whom body weight was measured before surgery and on the first or second postoperative day.

ASA = American Society of Anesthesiologists; BMI = body mass index; NNISS = National Nosocomial Infections Surveillance System[19]; SENIC = Study on the Efficacy of Nosocomial Infection Control.[18]

We included a total of 231 patients, of whom 73 were morbidly obese. We also analyzed the incidence of postoperative complications for the different BMI groups because it was thought there may be important differences in intervention effect, but this was not found. However, because only 34% of the patients were morbidly obese, the effect of high oxygen on this specific group needs to be investigated further.

The overall frequency of SSI was 29%, which is somewhat higher than had been reported previously in obese patients.[20] The frequency of SSI after laparoscopic and endoscopic bariatric surgery recently was found by Birkmeyer *et al.* to be 3.2%,[21] whereas Merkow *et al.*[22] found an incidence of approximately 15% after colectomy for cancer. The higher frequency in our study probably is caused by a high number of acute procedures, increased comorbidity, and intraoperative contamination. SSI was detected with thorough follow-up according to the sensitive criteria by the Centers for Disease Control and Prevention, which recently has been shown to be a

Table 2. Clinical Outcomes for 213 Obese Patients Scheduled for Laparotomy

	80% Oxygen Group (n = 102)	30% Oxygen Group (n = 111)	Univariate Odds Ratio [95% CI]	*P* Value	Adjusted Odds Ratio* [95% CI]	*P* Value
Surgical site infection	32 (31%)	29 (26%)	1.29 [0.71–2.34]	0.40	1.22 [0.63–2.39]	0.57
Superficial infection	16 (50%)	21 (73%)				
Deep infection	8 (25%)	5 (29%)				
Organ space infection	8 (25%)	3 (10%)				
Atelectasis	9 (8.8%)	7 (6.3%)	1.44 [0.52–4.01]	0.49	1.18 [0.41–3.43]	0.76
Pneumonia	6 (5.9%)	5 (4.5%)	1.33 [0.39–4.48]	0.65	1.05 [0.29–3.78]	0.94
Respiratory failure	8 (7.8%)	5 (4.5%)	1.80 [0.57–5.71]	0.32	1.58 [0.46–5.40]	0.47

Values are N (%) or median [5–95% range].

* Adjusted for center, diabetes mellitus, acute surgery, chronic obstructive pulmonary disease, current smoker, upper abdominal incision, duration of surgery, and age (older/younger than 40 yr) where possible.

suitable standard definition for identifying SSI.[23] Our observed frequency of SSI was comparable with a study by Cantürk *et al.,* who reported SSI in 29% of 61 obese and extremely obese patients undergoing general elective surgery.[3]

The frequency of SSI among the patients in the PROXI Trial (median BMI = 25 kg/m^2, interquartile range = 22–28 kg/m^2) was 20%,[10] compared with the 29% found in this subgroup analysis of the obese patients (BMI ≥ 30 kg/m^2). The distribution of SSI in the different weight groups among the patients in the PROXI Trial is shown in figure 2, which illustrates that the frequency of SSI appears to increase with increasing body weight. In addition to a higher frequency of SSI, the obese patients had a much higher frequency of rupture of the abdominal fascia, which underlines the compromised healing process in these patients. A recent retrospective study of 1,024 trauma patients showed a higher rate of nosocomial infections in obese patients and a significantly higher frequency of pneumonia and wound infections.[24] In that study, obese patients had a 4.7-fold higher risk of infection, and morbidly obese patients had an almost 6-fold higher risk of infection compared with patients with a BMI less than 30 kg/m^2. Obesity was still a risk factor for infection when controlling for age and comorbidity.

The increased risk of SSI among obese patients may also be caused by impaired immune system,[25] larger wound area, and longer operating time.[2] Another explanation is that the perioperative $Psqo_2$ is significantly reduced in obese patients during major abdominal surgery.[11] Even during supplemental oxygen administration, $Psqo_2$ remains at a lower than normal level of partial pressure, which is associated with a substantial risk of infection.[11] This increased risk is in accordance with the results of our trial and suggests that factors other than perioperative Fio_2 influence $Psqo_2$, such as hypercapnia,[26] body temperature,[27] supplemental fluid,[28] and the use of vasopressors and epidural analgesia.[29] However, these factors were all similar in the two groups. It is possible that long-term supplemental postoperative oxygen can reduce the incidence of SSI because it has been shown to significantly increase $Psqo_2$ when administered for an average period of 13 h after surgery.[30] However, the first hours after bacterial contamination traditionally have been recognized as critical for establishing the infection.[31]

Atelectasis is an important perioperative pulmonary complication. Two mechanisms contribute to atelectasis forma-

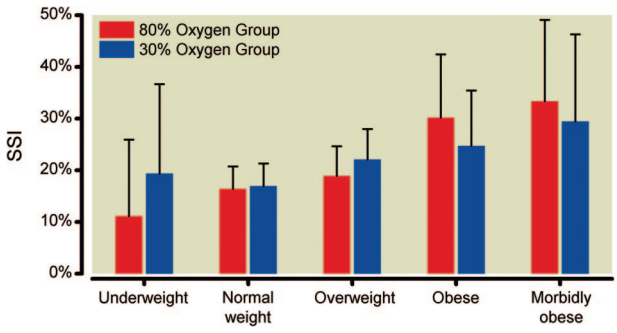

Fig. 2. Surgical site infection (SSI) in 1,386 patients scheduled for laparotomy. *Bars* indicate upper 95% CI. Underweight: BMI less than 18.5 kg/m^2; normal weight: BMI = 18.5–24.9 kg/m^2; overweight: BMI = 25.0–29.9 kg/m^2; obese: BMI = 30.0–34.9 kg/m^2; morbidly obese: BMI ≥ 35.0 kg/m^2. BMI = body mass index.

Table 3. Adverse Events Other than Primary and Secondary Outcomes for 213 Obese Patients Scheduled for Laparotomy

	80% Oxygen Group (n = 102)	30% Oxygen Group (n = 111)
Postoperative hospitalization, days	6 [1–35]	5 [2–45]
Admission to intensive care unit	11 (10%)	9 (8.1%)
Abdominal reoperation	22 (22%)	21 (19%)
30-day mortality	1 (1.0%)	3 (2.7%)
Any adverse event	52 (51%)	58 (52%)
Wound related	18 (18%)	20 (18%)
Any serious adverse event	22 (22%)	22 (20%)
Sepsis	4 (3.9%)	3 (2.7%)

Values are expressed as N (%) or median [5–95% range]. An adverse event was considered serious if it was fatal, life threatening, caused permanent disability, or required prolonged hospitalization.

tion: compression and absorption.[32] Atelectasis leads to a ventilation-perfusion mismatch[33] and may predispose the patient to other pulmonary complications. Within minutes, ventilation with 100% oxygen results in significantly larger areas of atelectasis than does ventilation with 80% oxygen.[34] However, one trial by Akça *et al.* of 30 nonobese patients showed only a small, nonsignificant difference in the degree of atelectasis when an inspiratory perioperative F_{IO_2} of 80% was given compared with 30% oxygen.[35] The frequency of atelectasis among the patients in the PROXI Trial was 8% *versus* 7% in the 80% and 30% oxygen groups, respectively, and 6% in both the 80% and the 30% oxygen groups experienced pneumonia.[10] Another subgroup study of the PROXI Trial involving 35 patients showed no significant difference in change in oxygenation index or functional residual capacity when 80% oxygen was administered than when 30% oxygen was used.[36]

Less evidence of the effect of ventilation with high oxygen is available in obese patients, but morbidly obese patients are more prone to perioperative atelectasis formation, and the atelectasis remains unresolved for a longer period after surgery than occurs in nonobese patients.[1] One recent study of 142 moderately obese patients found a minimal reduction in postoperative lung function when patients were given 80%, compared with 40%, oxygen during minor peripheral surgery.[37] The study showed a tendency toward better spirometry values in the low oxygen group and better arterial saturation during the first 2 h. We were not able to find any significant differences in the incidence of atelectasis, pneumonia, or other respiratory complications when given 80% oxygen compared with 30% oxygen. Moreover, there were no significant differences between obese and morbidly obese patients with regard to the secondary outcomes.

We examined only patients with pulmonary symptoms, and a chest radiograph or computed tomography was taken when relevant. Therefore, a difference in the frequency of subclinical atelectases could have been overlooked in this study, but if present, these subclinical atelectases did not result in significant differences in pneumonia or respiratory failure. One recent study found that a recruitment maneuver followed by positive end-expiratory pressure reduced atelectasis and improved oxygenation in morbidly obese patients.[38] However, a positive end-expiratory pressure of 10 cm H_2O alone did not reduce atelectasis. We did not measure the use of recruitment maneuvers followed by positive end expiratory pressure; however, we believe the use of this combination was limited and thus not a bias to the results.

We used the preoperative calculated BMI as inclusion criteria. This formula could have been a limitation, particularly if applied to individuals with a great muscle mass, in whom body fat percent may be a more accurate measurement in regard to SSI.[39] For pulmonary complications, an evaluation of body fat distribution as upper body fat distribution or central obesity may have been a more accurate measurement.[40,41] It is also possible that some patients have had a significant amount of ascites or tumor mass removed during surgery, resulting in a falsely high BMI. However, BMI is easy to measure and allows for comparison with other trials. The change in body weight at the first postoperative day was similar in the two groups (table 1).

We included a large number of obese patients undergoing open abdominal surgery, including 18% acute procedures. We had a thorough follow-up with assessment of adverse events in all patients. Thus, we believe the results of this study are generalizable to a general obese surgical population undergoing laparotomy, including acute laparotomy and gynecologic cancer surgery.

In summary, our trial, which included more than 200 obese patients undergoing acute or elective abdominal surgery, did not find a reduction in the frequency of SSI when 80% oxygen was given. Moreover, we did not find a significant association between perioperative F_{IO_2} and the incidence of pulmonary complications or other adverse events.

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