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Effect of High Perioperative Oxygen Fraction on Surgical Site Infection Following Surgery for Acute Sigmoid Diverticulitis. A Prospective, Randomized, Double Blind, Controlled, Monocentric Trial

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Rezumat

Efectul administrării perioperatorii de oxigen cu fracție inspiratorie crescută asupra infecțiilor postoperatorii de plagă în tratamentul chirurgical al diverticulitei sigmoidiene acute. Un studiu prospectiv, randomizat, dublu-orb, controlat, monocentric

Scop: Rolul clinic al hiperoxigenării în prevenția infecțiilor postoperatorii la nivelul plăgii (SSI) rămâne incert în condițiile în care studiile randomizate pe aceasta temă au raportat rezultate diferite. Unul dintre motivele de bază din spatele acestor rezultate contradictorii poate fi acela că studiile precedente au inclus populații heterogene de pacienți și seturi de proceduri diferite. Scopul studiului prezent este de a evalua influența hiperoxigenării asupra SSI într-opopulație omogenă.
Metode: Am efectuat un studiu prospectiv randomizat, în perioada Ianuarie 2009 - Mai 201, incluzând 85 de pacienți la care s-a efectuat anastomoză intraperitoneală pentru diverticulită sigmoidiană acută, prin abord chirurgical deschis. Pacienții au primit în mod randomizat oxigen/amestec gazos cu fracție inspiratorie (FiO_2) de 30% (n=43), respectiv 80% (n=42). Administrarea s-a inițiat după inducerea anesteziei și s-a menținut 6 ore după operație.
Rezultate: Procentul total de infecții postoperatorii ale plăgii a fost de 24,7% (21 din 85 de cazuri), după cum urmează: 14 pacienți (32,5%) din grupul cărora li s-a administrat oxigen cu fracție inspiratorie 30% FiO_2 și 7 (16.6%) din grupul cu 80% FiO_2 ($p < 0.05$). Riscul de SSI a fost cu 43% mai redus în grupul cu 80% FiO_2 (RR, 0.68; 95% interval de încredere, 0.35-0.88) comparativ cu grupul primind oxigen cu 30% FiO_2.
Concluzii: Prin urmare, administrarea de oxigen cu fracție inspiratorie 80% FiO_2 în timpul operației și 6 ore după încheierea acesteia în cazul diverticulitei sigmoidiene acute, în vederea reducerii ratei de SSI, ar trebui luată în considerare ca parte a metodelor de îmbunătățire a calității serviciilor chirurgicale, fiind asociată cu puține riscuri pentru pacienți și costuri suplimentare reduse.

Cuvinte cheie: diverticulită sigmoidiană acută, oxigen cu fracție inspiratorie

Abstract
Propose: The clinical role of hyperoxiato prevent postoperative surgical site infection (SSI) remains uncertain since randomized controlled trials on this topic have reported different results. One of the principal reasons for such mixed results can be that previous trials have entered a heterogeneous population of patients and set of procedures. The aim of our study was to assess the influence of hyperoxygenation on SSI usingan homogeneous study population.

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Methods: We studied, in a prospective randomized study, extended on a time interval January 2009 to May 2015, 85 patients who underwent open intraperitoneal anastomosis for acute sigmoid diverticulitis. Patients were assigned randomly to an oxygen/air mixture with a faction of inspiration (FiO2) of 30% (n=43) or 80% (n=42). Administration was started after induction of anesthesia and maintained for 6 hours after surgery.
Results: The overall wound site infection rate was 24.7% (21 out of 85): 14 patients (32.5%) had a wound infection in the 30% FiO2 group and 7 (16.6%) in the 80% FiO2 group ($p < 0.05$). The risk of SSI was 43% lower in the 80% FiO2 group (RR, 0.68; 95% confidence interval, 0.35-0.88) versus 30% FiO2.
Conclusions: Therefore, supplemental 80% FiO2 during and 6 hours after open surgery for acute sigmoid diverticulitis, reducing post-operative SSI, should be considered part of ongoing quality improvement activities related to surgical care, accompanied by few risk to the patients and little associates cost.

Key words: acute sigmoid diverticulitis, oxygen fraction

Introduction

Colorectal operations are, at best, clean-contaminated procedures, and at times there is contamination of both the peritoneal cavity and the surfaces of the surgical wound. In addition, the diseases of the large bowel that requires surgery-tend to afflict elderly patients. Collectively, the combination of an unclean environment, major surgery and debilitated patients creates a situation that is associated with a very high incidence of wound infection. In open colorectal surgery the incidence of surgical site infection (SSI) varies from 2-25% and is associated with body mass index (BMI) ≥30, creation/revision/reversal of an ostomy closure, perioperative transfusion, male gender, and ASA score ≥3 (1-2). The incisional SSI rates in colon (n=339) and rectal (n=217) resections were 9.4% and 18% respectively (p=0.0033).

Risk factors for SSI in colon surgery were ostomy closure (OR=7.3) and lack of oral antibiotics (OR=3.3), while in rectal surgery, risk factors were perioperative steroids (OR=3.7), preoperative radiation (OR=2.8) and ostomy creation (OR=4.9) (3).

Several interventions have been investigated as part of an evidence-based approach to reducing surgical site infections (SSIs): the use, timing, route and dosing of prophylactic antibiotics (4-7); the use of WBC-depleted RBC transfusions (8-11); the avoidance of hair shaving (12); the prevention of intraoperative hypothermia (13); and the use of mechanical bowel preparation (14,15). Despite these measures, significant clinical and economic burden of SSIs persists (16).

The use of supplemental perioperative oxygen has also been investigated, specifically in elective colorectal surgery patients, with conflicting reports regarding to its effectiveness in reducing SSIs (17-21).

One of the principal reasons for such mixed results may be that prior trials have entered a heterogeneous study population and set of procedures, which may have precluded the discovery of small but important differences.

To overcome this problem, we performed a prospective, randomized, controlled trial in a patient population with a single diagnosis (acute sigmoid diverticulitis), using one standard surgical approach (open colorectal resection through a midline laparotomy). Hence, the aim of our study was to obtain satisfactory statistical information considering the effects of hyperoxygenation on SSI, in a relatively homogeneous study population.

Materials and Methods

From January 2009 to May 2015, we studied, in a prospective randomized study, 81 patients consecutively (47 men, 38 women; mean age 68.9 years), who underwent elective open colorectal resection for acute sigmoid diverticulitis.

All patients underwent an initial helical computerized tomography (CT) scan of the abdomen and pelvis. Based on radiological findings, patients were stratified into five main groups (modified Hinchey classification). In the group of patients classified as Hinchey 0, the CT scan showed diverticulosis of the sigmoid colon with thickening of the main colonic wall and/or of the pericolonic fat layer (fat stranding) and no other abnormal radiological findings. In patients classified as Hinchey I, the CT scan showed pericolonic abscess formation or soft tissue inflammation and phlegmon. In patients classified as Hinchey II, the CT scan showed an additional pelvic or retroperitoneal abscess. In the last group of patients, classified as Hinchey III-IV, the CT scan showed the presence of free air and intraperitoneal fluid.

The indications for elective or semi-elective surgery included patients with antecedents of two or more previous acute attacks, treated conservatively; patients with one attack but associated with a contained perforation, or with a fistula; patients with a suspicious colonic carcinoma that cannot be excluded, and finally, patients with less than 50 years old and a single attack.

Exclusion criteria included expected surgery time of less than 1 hour, stage III and IV of Hinchey classification, diabetes mellitus (type 1 or 2), known immunological dysfunction (advanced liver disease, HIV infection, hepatitis C virus infection), weight loss exceeding 20% in the last 3 months, serum albumin concentration of less than 30 g/L, and a leukocyte count of less than 2500 cells/mL. During hospitalization, the patients were not givenantispastic drugs, steroids, or non-steroidal anti-inflammatory drugs (NSAIDs), apart from NSAIDs delivered IV.

Medical history was recorded, and a systematic physical examination was performed preoperatively. Patients were considered to have respiratory diseases, when they had a history of chronic obstructive pulmonary disease (COPD), asthma requiring routine care, or other clinically significant respiratory impairment. The patients were classified as grade I, II or III, according to the American Society of Anesthesiologists (ASA) grading system (22). (Table 1) The severity of sepsis was valued by APASH II score (Acute Physiologic and Chronic Health Evaluation) and MPI score (Mannafeim Peritonitis Index) (23,24)

The infection was assessed with the NNISS (National Nosocomial Infections Surveillance System) and the SENIC (Study on the Efficacy of Nosocomial Infection Control) scales (25,26). The NNISS and SENIC scoreshave been extensively evaluated, and larger values with these scores indicate a greater risk of infection.

In the SENIC scoring system (26),1 point is given for each of:

A. presence of 3 or more diagnosis;
B. surgery lasting longer than 2 hours;
C. operation classified as contaminated or dirty-infected;
D. abdominal surgery.

In the NNISS scoring system (25),1 point is given for:

A. ASA score of 3, 4 or 5;
B. operation classified as contaminated or dirty-infected;
C. operation lasting longer than expected regarding the operative performed procedure.

Mechanical bowel preparation was not performed. Management of diverticulitis included no food or drink orally, intravenous fluid resuscitation (normalsaline or Ringer's Lactate solution) and intravenous antibiotics (Ceftriaxone: 2 gr i.v. every 24 hours and Metronidazole: 500 mg i.v. every eight hours). Prophylactic subcutaneous heparin was administered and given daily until discharge from hospital.

Anesthesia was obtained using the same procedure for all patients. Preanesthesia was accomplished using atropine (0.01 mg/Kg) and promethazine (0.5 mg/Kg), induction using sodium thiopental (5 mg/Kg) and atracurium (0.5 mg/Kg), followed by tracheal intubation and assisted ventilation using nitrogen dioxide (NO2)/oxygen (O2) 2:1. After intubation, anesthesia was maintaned with oxygen in air, sevoflurane and remifentanil (0.25 μg/Kg/min).

The randomization envelopes were opened in the operating department after induction of anesthesia by the anesthesiologist. Patients were assigned to an oxygen/air mixture with a fraction of inspired oxygen (FiO2) of 30% (Group 1) or 80% (Group 2). The displays of the anesthesia machine and gas monitors were covered with cardboard shields in both the operating department and postanesthesia care unit to keep the surgical team blinded to group assigned.

The Ethical Committee of the Department of Surgery at the University of L'Aquila approved the study protocol. All patients gave informed written consents.

The surgical technique consisted of a midline laparotomy. Sigmoid colon was removed entirely with mobilization of splenic flexure, avoiding problems of tension. Division of the rectum was carried out with a linear endoscopic 45-mm Roticulator stapler. The anastomosis was fashioned with a mechanical circular stapler, usually 31 mm and occasionally 29 mm in diameter, according to the double-stapled technique (end-to-end transanal colorectal anastomosis). Peritoneal lavage was performed with at least 4 litersof warm normal saline or until the fluid aspirated come back clear.

The surgical wound, in all patients, was meticulously irrigated and sutured with absorbable sutures. The skin was closed using non absorbable sutures (silk).

Electrocardiogram, heart rate, noninvasive blood pressure, FiO2, pulse oxymetry (SpO2), and end-tidal concentrations of carbon dioxide and sevofluranewere continuously monitored during the surgery. An arterial blood sample was obtained 1 hour after induction of anesthesia to evaluate partial pressure of oxygen (PaO2); another sample was obtained 2 h after extubation.

When the operation was finished, the inhaled anesthetic was stopped and FiO2 was increased to 100% during extubation. During the first six postoperative hours, all patients were administered non-rebreathing facemasks with a reservoir (Intersurgical, Wokingham, Berkshire); oxygen was provided at the randomly designated concentration at a total flow of 16 L/min. Subsequently, patients breathed ambient air, although supplemental oxygen was provided if necessary, to maintain oxygen saturation of at least 92% as measured by pulse oxymetry. An intention-to-treat analysis was performed, and patients who required a transient increase in inspired oxygen concentration were included in the analysis. Perioperative normothermia was maintained with circulating-water mattresses and forced-airheaters. Fluids were administered intraoperatively at a rate of 20 mL/Kg per hour; blood loss was restored with crystalloids or colloids and, only when necessary, with blood-transfusion. Fluid was administered at 5 mL/Kg per hour during the first 6 postoperative hours and then reduced to 3 mL/Kg per hour only when patients were transferred to the ward. In the postoperative anesthesia care unit (PACU), vital signs (blood pressure, pulse, respiration, pulse oximetry and adequate answering) were monitored every 15 min. Patients were discharged from PACU when vital signs were normalized. We used a prophylactic multimodal analgesic technique for treatment of postoperative pain. Thus, patients received incisional local anesthetics using a total of 20 ml (100 mg) of bupivacaine (0.5 % bupivacaine). Intravenous ketorolac trometamine (30 mg), was given every 6 hours on the first 2 days after operation, and after ward on demand.

Surgical wounds were assessed daily for infection by surgeons who were unaware of patients'corresponding treatment groups.

Wound infections were graded using a classification described elsewhere (27). Wound infections were considered grade 1 with the presence of erythema, indurations, and pain; grade 2, same as grade 1 but with serous fluid; grade 3, the presence of contaminated fluid in less than half the wound; grade 4, same as grade 3 but contaminated fluid in more than half the wound. Wound dehiscence was considered to be present when surgical closure of the cutaneous or subcutaneous tissue (superficial) or the fascia and muscular plane (deep) was necessary in the early postoperative period.

Wounds were considered infected when they met Centers for Disease Control and Prevention definitions (28). Purulent exudates were cultured and, when positive for pathogenic bacteria, appropriate antibiotic treatment was initiated. Only those infections diagnosed during the first 14 postoperative days were included.

Wound healing characteristics were also evaluated using the ASEPSIS score (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, and duration of inpatient Stay) (29). This is an established and validated system that is derived from the weighted sum of points assigned for the following factors: duration of antibiotics administration; drainage of pus with the patient under local anesthesia; debridement of the wound with the patient under general anesthesia; serous discharge; erythema; purulent exudate; separation of deep tissues; and hospitalization exceeding 14 days. A daily score of 20 or more was considered evidence of infection (30). Discharged patients were observed in the outpatient surgical clinic to assess wound status on day 15.

Anastomotic leakage was defined before the beginning of the study as either:

A. Radiological: demonstration of contrast extravasation on abdominal computed tomography scans with triple contrast or by gastrografin enema;
B. Causing diffuse peritonitis: presence of fecal fluid at relaparotomy;
C. Causing local sepsis: presence of a localized abscess in the vicinity ofan anastomosis;
D. Fecal discharge from the drain/wound.

In practice, we did not perform any routine contrast enema in asymptomatic patients, but we had a low threshold for abdomen/pelvic imaging with triple contrast CT scan in patients with suspected anastomotic leak, either clinically (pain, fever, abdominal tenderness, prolonged ileus) or biologically (persistently elevated white blood cells or C-reactive protein).

Statistical analysis

Independent medians were compared with the Mann-Whitney U test and paired medians with the Wilcoxon test or Friedman test for more than two variables. Proportions were compared with Fisher's exact test, the likelihood ratio test or Pearson's X2 test as indicated. All P values are two tailed. Statistical analysis was performed using SPSS® version 13.0 for Windows (SPSS; Chicago, Illinois, USA).USA).

The risk of SSI associated with potential risk factors was determined by calculating the cumulative incidence. To evaluate the relationship between the FiO2 group and other potentially predictive factors and wound infection, the respective relative risks (RRs) were calculated. Finally, a logistic regression analysis was performed to determine the effect of 80% FiO2 adjusted for the remaining potential risk factors for wound site infection. Those variables with $p < 0.25$ in the univariate (simple) analysis were included in the multivariate logistic regression analysis. These variables included sex, weight, age, coexisting respiratory disease, hemoglobin, glucose, and SENIC score.

Manipulation of variables in the model was performed using the Enter method, which forces the introduction of all the variables of interest under the specified criteria.

The goodness-of-fit of the model was evaluated with the Hosmer-Lemeshow method.

Results

We collected data from 85 patients who were enrolled and randomized: 43 received 30% perioperative oxygen and 42 received 80% perioperative oxygen. In *Fig. 1*, the CONSORT analysis is described in details. (31) Morphometric, demographic, modified Hinchey classification and other preoperative characteristics were similar in the 2 treatment groups (*Table 1*). There was no significant difference in the nutrition status between the two groups. Nutritional status was assessed by means of Nutrition Risk Screening 2002 (NRS) or Kondrup Score based on age, recent weight loss, BMI, severity of disease and planed surgical intervention (32). Other than the percentage of inspired FiO2 and resulting PaO2, there were no significant differences between the groups.

Other than postoperative hemoglobin, all physiological variables, a rigorous perioperative care (adequate fluid administration, maintenance of normothermia), and laboratory test results data (including blood glucose concentration), were also similar during the postoperative period through hospital

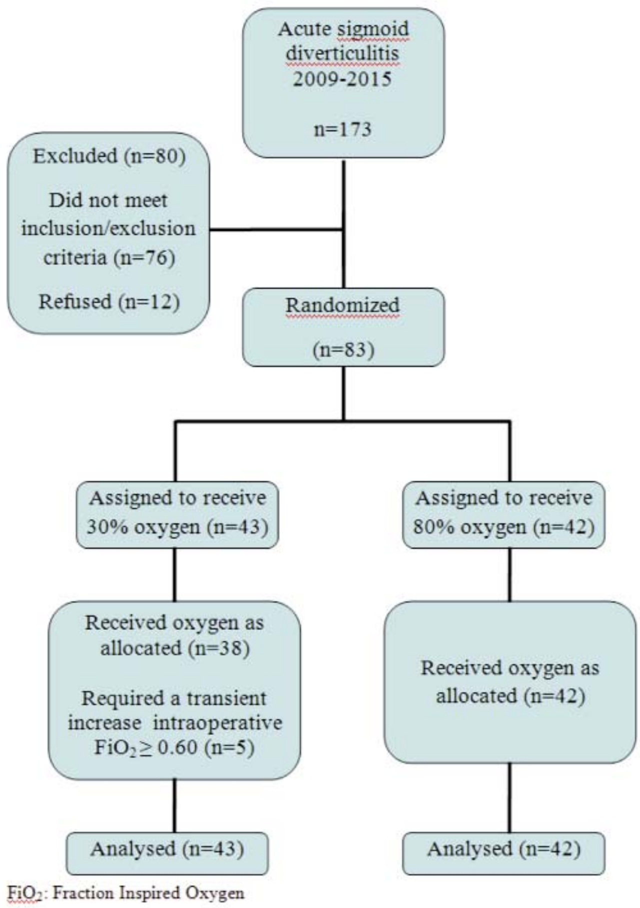

Figure 1. *Trial profile: CONSORT analysis*

Table 1. Comparison of patient characteristics in the two groups

Preoperative	30% FiO_2 (N=43)	80% FiO_2 (N=42)
Age, y, mean (range)	68.6 (49-86)	71.4 (55.92)
Sex ratio (M:F)	24:19	23:19
Body mass index, mean (range)	24.4 (17.1-37.9)	25.8 (18.4-36.2)
Modified Hinchey Classification No (%)		
Grade 0	1(2.3)	1(2.3)
Grade I	14 (32.5)	14 (33.5)
Grade II	28 (65.1)	27(64.2)
Hemoglobin g/L, mean (range)	13.2(11.8-15.9)	13.8(11.6-16.1)
ASA grade No (%)		
I	1 (2.3)	2 (4.7)
II	18(41.8)	17(40.4)
III	24(55.8)	23 (54.7)
Risk Score No (%)		
SENIC		
1	13(30.2)	12(28.5)
2	23(53.4)	22 (52.3)
3	5 (11.6)	6 (14.2)
4	2 (4.6)	2 (4.7)
NNISS		
0	19 (44.1)	18(42.8)
1	17 (39.5)	17 (40.4)
2	6 (13.9)	5 (11.9)
3	1 (2.3)	2 (4.7)

Table 2. Acute Sigmoid Diverticulitis: surgical data

	30% FiO_2 (N=43)	80% FiO_2 (N=42)
Duration of operation, min, mean (range)	195(100-385)	200 (95-410)
Type of operation:		
Primaryanastomosis	43	42
Protectiveloopileostomy	9	11

Table 3. Intraperitoneal anastomosis (85 patients): wound infection (21 pts=24.7%)

	30% FiO_2 (N=43)	80% FiO_2 (N=42)	P
Wound infection	14 pts (32.5%)	7 pts (16.6%)	<0.05
Grade 1	1 pt	1 pt	
Grade 2	6 pts	4 pts	
Grade 3	5 pts	2 pts	
Grade 4	2pts	/	
ASEPSIS score ≥20	7 pts (16.2%)	3 pts (7.1%)	<0.05

ASEPSIS: Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, and duration of inpatient Stay.

*Table 4. Factors associated with surgical site infection (Adjusted and Unadjusted Analysis)**

	RR (95% CI)	
	Unadjusted Univariate Analysis	Adjusted Multivariate Analysis
80% FiO_2	0.68(0.35-0.88)	0.45(0.21-1.04)
Male sex	1.94(1.04-3.58)	2.03(0.89-4.88)
Weight (Kg)	1.03(0.96-1.05)	1.01(0.96-1.04)
Age (y)	1.04(0.92-1.06)	1.02(0.96-1.06)
Hinchey grade II	2.04(2.06-3.94)	3.16(1.94-7.80)
Respiratory disease	2.14(1.04-4.76)	3.22(1.98-9.80)
Preoperative hemoglobin (g/L)	1.18(0.98-1.46)	1.08(0.88-1.38)
Preoperative glucose (mg/dL)	1.01(0.94-1.04)	1.01(0.94-1.03)
Senic Score		
1	1	1
2	1.12(0.58-2.20)	1.06(0.46-2.96)
3	1.18(0.48-2.72)	2.05(0.48-8.98)

RR= Relative Risk; CI= Confidence Interval; FiO_2= Fraction of inspired oxygen
SENIC= Study of the Efficacy of Nosocomial Infection Control
*Categorical variables include FiO2, male sex, respiratory disease, and SENIC store. Continuous variables include weight, age, preoperative hemoglobin, and preoperative glucose concentration.

discharge.

The mean duration of surgery was 195 minutes (range 100-385) in patients assigned to 30% oxygen and 200 minutes (range 95-410) in those assigned to 80% oxygen (p=0.90) (*Table 2*). Referring to 85 operations for sigmoid acute diverticulitis: 2 (2.3%) were Hinchey grade 0; 28(32.9%) Hinchey grade I; 55 (64.7%) Hinchey stage II.

We performed 85 colonic resections followed by end-to-end transanal mechanical colorectal anastomosis. 20 patients (23.5%) underwent protective loop ileostomy (*Table 2*), depending on the surgeon's technical evaluation of the quality of the anastomosis.Therefore, we performed in 65 patients a single-stage procedure, and in 20 patients a two-stage procedure.

The overall wound infections rate was 24.1% (21 out of 85) (of these, 7 patients had positive cultures for pathogenic bacteria): 14 patients (32.5%) had a wound infection in the 30%FiO2 group and 7 (16.6%) in the 80% FiO2 group. Wound infection was significantly lower in the 80% FiO2 group of patients than in the 30% FiO2 group of patients ($p<0.05$) (*Table 3*). The grade of wound infection are also reported in *Table 3*. ASEPSIS score exceeding 20 on an postoperative day was significantly lower in the 80% FiO2 group of patients than in the 30% FiO2 group of patients ($p<0.05$) (*Table 3*). The risk of SSI was 43% lower in the 80% FiO2 group (RR, 0.68; 95% confidence interval (CI), 0.35-0.88) vs 30% FiO2 group (*Table 4*).

Five of 43 patients (11.6%) in the 30% oxygen group required a FiO2 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. These patients who required a transient increase in inspired oxygen concentration did not have wound infection.

Patients with infection had mean (SD) ASEPSIS score on the first 6 postoperative days of 9.2 (0.89), whereas those without infections had mean (SD) score of 4.8 (0.42) (p=0.002). Patients with infection took longer to ambulate (mean (SD), 5.6 (3.8) vs3.2 (2.6) days; p=0.006), had their staples later removed (12.1 (3.6) vs 10.1 (2.9) days; p=0.008), and had longer hospital stays (18.2 (8.9) vs 10.2 (4.2) days; p=0.001).

In unadjusted univariate analyses, men, Hinchey grade II and those with coexisting respiratory disease were at increased risk of SSI (RR, 1.94; 95% CI, 1.04-3.58; RR, 2.04; 95% CI, 2.06-2.94; and RR, 2.14; 95% CI, 1.04-4.76; respectively) (*Table 4*). After multivariate adjustment, only the percentage of inspired oxygen, Hinchey grade II and coexisting respiratory disease were significantly associated with the risk of infection. After adjustment for all covariates, the risk of SSI was reduced 50% in patients assigned to 80% oxygen (RR, 0.45; 95%CI; 0.21-1.04; $p<0.05$). Patients with coexisting respiratory disease and with grade II, had a 3.22-fold (95% CI, 1.98-9.80) and 3.16-fold (95% CI, 1.94-7.80) greater probability of SSI respectively (*Table* 4).

In multivariate analysis (*Table* 5), ASA score ≥ 3, a prolonged operative time, and BMI ≥ 30 were not significantly associated with a higher risk of wound infection.

The overall anastomotic leak rate was 18.8% (16 out of 85): 11 patients (25.5%) had an anastomotic dehiscence in the 30% FiO2 group and 5 (11.9%) in the 80% FiO2 group ($p<0.05$) (*Table* 5). Five of 43 patients (11.6%) in the 30% oxygen group required anFiO_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. These patients who required a transient increase in inspired oxygen concentration, do not have an anastomotic dehiscence. The risk of anastomotic leakage was 44% lower in the 80% FiO2 group (RR, 0.65; 95% confidence interval (CI), 0.44-0.96) versus the 30% FiO2. In the patients with anastomotic dehiscence, the overall wound infections rate was 18-7% (3 out of 16): 2 patients (18.1%) had wound infections in the 30% FIO2 group and 1 (20%) in the 80% FIO2 group. this difference was not statistically significant ($p = 0.122$). Nine patients had to be admitted in the intensive care unit immediately after the operation because of postsurgical complications. Five patients died during the study period. The mortality rate associated with anastomotic leak was 18.7% (3 out 16). These patients were assigned to the 30% oxygen group (*Table* 5). Two patients died because of cardiovascular diseases (myocardial infarction and pulmonary embolism). One patient of them was assigned to the 30% oxygen group (myocardial infarction) and one to the 80% oxygen group (pulmonary embolism). Three (18.1%) patients with an anastomotic leakage needed a reoperation for fecal diversion (*Table* 5). The median delay between the first operation and the return to the operating room for anastomotic leak was 7 and 9 days

Ten patients were conservatively treated with CT-scan-guided radiological drainage and antibiotics (five patients for each group) (*Table* 5).

Table 5. *Intraperitoneal anastomosis (85 patients): anastomotic dehiscence (16 patients=18.8%)*

	30% FiO_2 (N=43)	80% FiO_2 (N=42)	P
Anastomotic dehiscence	11 pts (25.5%)	5 pts (11.9%)	<0.05
Mortality	3 pts	/	
Reoperation for fecal diversion	3	/	
CT-scan-guided radiological drainage and antibiotics	5	5	

Discussion

Surgical Site Infections (SSIs) are among the most common postoperative complications in patients who have undergone colorectal surgery. The occurrence of an SSI results in reduced quality of life, increased hospital length of stay, increased likelihood of mortality, and markedly increased cost (33-36).To prevent surgical site infection, it is essential to optimize perioperative conditions in the first hours following bacterial contamination (37).

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 epithelization (38-40). Perioperative arterial and wound oxygen tension can be increased by a higher inspiratory oxygen fraction (46). Two trials have suggested that high (80%) FiO2 is effective in preventing surgical wound infections, with relative risk ratios of 39% (17) and 54% (18). In contrast, 4 other trials (19,40,41,42) did not report a significant reduction; one trial was stopped early because the frequency of surgical wound infections doubled (24), one was statistically insignificant (19), one, a large trial investigating a high oxygen fraction delivered via non-rebreathing face mask to prevent postcesarean surgical site infection was stopped for futility (41), and recently, the PROXI trial affirmed that the relative risk reduction was only the 5% in favor of 80% oxygen group (42).

To date, there are five meta-analysis published to collate the effect of supplemental perioperative oxygen on SSI after colorectal surgery (43-47). Chura et al (43), Al-Niaimi et al (45) and Qadanet al (47) affirmed that high-concentration of supplemental perioperative oxygen is associated with a lower risk of SSI in patients undergoing colorectal surgery, whereas Braret al (44) concluded that high perioperative oxygen fraction in colorectal surgery does not significantly reduce SSI.

In a recent meta-analysis Togioka et al (46) affirmed that perioperative high inspired oxygen therapy overall was not found to be beneficial for preventing SSI, whereas the positive results of 2 subgroup analyses (general anesthesia and colorectal surgery trials) suggest a benefit for hyperoxia in decreasing surgical site infection.

The reasons for such controversial data are most likely multifactorial. The use of different SSI definitions may in part be responsible for such discrepancy (48).Another aspect is the interplay of different factors that are need for wound healing such as normothermia and adequate fluid supply. Without strict adherence to the optimal perioperative protocol, vasoconstriction may ensue and reduce the effect of tissue oxygenation (49).Standard methods of postoperative care are also important factors (43).Statistical consideration such as power calculation for sample size can also affect the data interpretation (47).

The most important factor, in our opinion, that explains the mixed literature, is the heterogeneity of the different study populations (20), including mixed types of diseases and operative procedures (gastrointestinal tract, gynecological, and even colorectal surgery) that are associated with various types of perioperative anesthetic care (42). Our study population is relatively homogeneous in contrast to the recently published randomized, controlled studies dealing with supplemental oxygen and SSI as it includes a single diagnosis (sigmoid acute diverticulitis), one type of operation (elective open colo-rectal resection with intraperitoneal anastomosis) (*Table 2*), uniformity of the surgical wound (midline laparotomy) and for age, sex, BMI, ASA grade, tumor stage, risk of infection (NNISS and SENIC scales) (*Table 1*).

In our randomized trial of 80% vs 30% inspired supplemental oxygen in the intra-operative and postoperative period (six hours after surgery), we found that 80% supplemental oxygen reduced the risk of SSI by 43%. When controlling for multiple contributing factors, the reduction in SSI risk associated with 80% FiO2 was nearly 50%. Patients with wound infections had significantly longer hospital stays and delays to ambulation. This observed risk reduction was similar to the 2-fold reduction reported by Greif et al (18), in 500 patients and also consistent with the studies by Hopf et al (40) and Belda et al (17), showing that risk of infection is inversely related to tissue oxygenation.

Moreover, our study suggest that high (80%) FiO2 is effective in preventing anastomotic leakage according to other trials (50,51).

All surgical wounds become contaminated to some degree. The primary determinant of whether contamination is established as a clinical infection is host defense. Host defense is mostly critical during a decisive period lasting a few hours after contamination. For example, antibiotics ameliorate infections and hypoperfusion aggravates infections only during the first few hours after contamination (52). The decisive period for oxygen remains unknown but may be for longer than for antibiotics. There were various reasons for administering oxygen for 6 hours after surgery (53). It was known from previous studies that the relative anastomotic ischemia was transitory (54,55) and limited to the first 24 hours after surgery. Patients may tolerate a mask that delivers a high oxygen concentration for a few hours after surgery, but such concentration would be difficult to maintain for longer periods owing to patient discomfort; for this reason the supplemental oxygen therapy was restricted to 6 hours after surgery. Garcia-Botello et al (51) have demonstrated that there were significant differences in anastomotic pH between the 30 minutes and 6 hours readings but not between the 6 and the 24 hours readings in both group, confirming that there is a relative transitory postoperative anastomotic hypoperfusion within the first 6 hours after surgery. Clinically reversible manifestations and physiological changes to breathing 100% oxygen have been shown to appear after at least 6-24 hours (56,57), with more severe changes after 30 hours. Our patients were maintained at the designated oxygen concentration during surgery and for 6 postoperative hours. There were no complications observed in our study that could be attributed to the administration of 80% oxygen for 6 hours after operation. In contrast, Greif et al (18) provided supplemental oxygen for only 2 postoperative hours. The results, however, were nearly identical, which suggest that 2 hours may be sufficient. Only a direct comparison within a single study will identify the optimal postoperative duration of supplemental oxygen therapy. Moreover, oxygen also improves immune function (58) and is an important factor for eradication of infection. Studies using experimental wound models have demonstrated that Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli injected into wounds could be eradicated at rates proportional to FiO2 or PO2 (59,60) and that antibiotics were increasingly effective at higher FiO2(59).

Conclusions

Therefore, supplemental 80% FiO2 during and for 6 hours after open surgery for acutesigmoiddiverticulitis, reducing surgical wound infections and postoperative anastomotic dehiscence, should be considered part ofongoing quality improvement activities related to surgical care, with few risks to the patient and little associated cost.

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