ORIGINAL ARTICLE

Perioperative Hyperoxygenation and Wound Site Infection Following Surgery for Acute Appendicitis

A Randomized, Prospective, Controlled Trial

Amitai Bickel, MD; Michael Gurevits, MD; Ronny Vamos, MD; Simon Ivry, MD; Arieh Eitan, MD

Objective: To assess the influence of hyperoxygenation on surgical site infection by using the most homogeneous study population.

Design: A randomized, prospective, controlled trial.

Setting: Department of surgery in a government hospital.

Patients: A total of 210 patients who underwent open surgery for acute appendicitis. In the study group, patients received 80% oxygen during anesthesia, followed by high-flow oxygen for 2 hours in the recovery room. The control group received 30% oxygen, as usual.

Intervention: Open appendectomy via incision in the right lower quadrant of the abdomen.

Main Outcome Measures: Surgical site infection, mainly assessed by the ASEPSIS (additional treatment, serous discharge, erythema, purulent discharge, separation of deep tissues, isolation of bacteria, and stay in hospital prolonged >14 days) system score.

Results: Surgical site infections were recorded in 6 of 107 patients (5.6%) in the study group vs 14 of 103 patients (13.6%) in the control group ($P=.04$). Significant differences in the ASEPSIS score were also found. The mean hospital stay was longer in the control group (2.92 days) compared with the study group (2.51 days) ($P=.01$).

Conclusion: The use of supplemental oxygen is advantageous in operations for acute appendicitis by reducing surgical site infection rate and hospital stay.

Trial Registration: clinicaltrials.gov Identifier: NCT01002365

Arch Surg. 2011;146(4):464-470

SURGICAL SITE INFECTION (SSI) constitutes a significant problem following elective and emergency operations and is the most common nosocomial infection in the surgical patient.[1] The postoperative infection rate approaches 10% to 20% following potentially contaminated surgery such as colorectal operations.[2] Besides being a medical problem per se, SSI is associated with significant prolongation of the hospitalization period and with the related economic aspects. The cause of SSI is multifactorial depending on the overall well-being of the patient, including nutritional, immunological, and hemodynamic status,[3-5] appropriate prophylactic antibiotics,[6,7] and fair operative technique.[8-10] Additional factors that influence SSI (and are sometimes controversial) include operative time, core body temperature, blood transfusions in proximity to surgery, postoperative pain, and tissue oxidative tension.[11]

In recent studies, the possibility of reducing SSI by perioperative hyperoxygenation has been raised, but the data obtained from the related randomized, controlled trials remain controversial. In 3 studies, perioperative inhalation of an oxygen-enriched (80%) mixture led to significant reduction of SSI following miscellaneous or only lower gastrointestinal tract surgery.[12-14] However, in another 3 randomized, controlled studies concerning various gastrointestinal tract, colorectal, or gynecological operations, perioperative hyperoxygenation was not associated with an improved rate of SSI.[15-18] However, in meta-analyses gathering almost all of the participating subjects (except the most recent article, by Meyhoff et al[18]), cumulative results favor the use of hyperoxygenation for SSI reduction.[19-21]

One of the principal reasons for such mixed results may be that prior trials have entered a heterogeneous population of patients and procedures, which may have precluded the discovery of small but im-

Author Affiliations: Departments of Surgery (Drs Bickel, Gurevits, Vamos, and Eitan) and Anesthesiology (Dr Ivry), Western Galilee Hospital, Nahariya, Israel.

portant differences. To overcome this problem, we performed a randomized, controlled trial in a patient population with a single diagnosis (acute appendicitis), using 1 surgical standard approach (open appendectomy through a McBurney incision in the right lower quadrant of the abdomen). Hence, the aim of our study was to obtain solid information considering the effects of hyperoxygenation on SSI following this procedure in a relatively homogeneous study population. In addition, as it is the most common emergent operation in surgery, reducing the SSI rate and convalescence time following acute appendicitis may carry the most significant economic gains.

METHODS

PATIENT CHARACTERISTICS

We performed a double-blinded, randomized, controlled trial of perioperative hyperoxygenation, with adult patients (aged >15 years) having an open appendectomy for acute appendicitis between November 1, 2006, and May 31, 2009. The operation was done through a McBurney incision in the oblique right lower quadrant of the abdomen. The decision to operate was based on clinical criteria (right lower quadrant pain, local tenderness, etc), blood test results, and results of imaging modalities (ultrasonography or abdominal computed tomography) suggestive of acute appendicitis. Written informed consent was obtained from each patient in accordance with the Declaration of Helsinki, and the study was approved by the local ethics committee. Parental consent was obtained when the patient was younger than 18 years.

All subjects were categorized as having an American Society of Anesthesiologists score of 1 or 2. Patients with chronic obstructive pulmonary disease, severe malnutrition (serum albumin concentration <3 g/dL; to convert to grams per liter, multiply by 10), or immunodeficiency disease were excluded from the study.

STUDY PROTOCOL

Preoperative antibiotics against gram-negative and anaerobic bacteria were given to all patients, including intravenous aminoglycosides (gentamicin sulfate, 5 mg/kg) and metronidazole (500 mg). When intraoperative findings indicated gangrenous or perforated appendicitis, antibiotic treatment lasted for 5 days. Anesthesia was introduced with fentanyl citrate (1-5 µg/kg), propofol (2 mg/kg) or thiopental sodium (4 mg/kg), and rocuronium bromide (0.5 mg/kg) or atracurium besylate (0.5 mg/kg), following preoxygenation by mask. Midazolam maleate was additionally prescribed (1-2 mg). Anesthesia was maintained with nitrous oxide with oxygen (in a ratio depending on group selection), isoflurane, 1%, rocuronium bromide or atracurium besylate (0.10-0.15 µg/kg), and fentanyl citrate (5-10 µg on demand). Ventilation was mechanically controlled at a frequency and tidal volume to maintain normocapnea. Adequate hydration and core temperature (measured in the distal esophagus) were strictly maintained during the operation and convalescence. Oxygen saturation was measured with pulse oximetry during anesthesia and the recovery period. Arterial blood for the measurement of partial pressure of oxygen was obtained after anesthesia was induced (before starting surgical manipulations), during surgery (just before wound closure), and 2 hours after recovery from anesthesia (before discharge to the department of surgery).

Randomization of the patients was stratified after the induction of anesthesia and endotracheal intubation, when each patient was assigned to 1 of 2 groups according to the selection of a sealed envelope by the anesthesiologist. In the control group, the patients received a mixture of 30% oxygen and 70% nitrogen, while in the study group, the fraction of inspired oxygen (F_{IO_2}) was 80% (combined with 20% air). In the recovery room following completion of the operation, the patients in the study group received high-flow oxygen (10 L/min) through a nonrebreathing mask with a reservoir for 2 hours, while a nasal cannula was used to deliver oxygen (4 L/min) in the control group. The surgeons were not informed about the mode of oxygenation. Following the recovery period, the data containing F_{IO_2} and arterial blood gas results were sealed in the envelope to be evaluated at the completion of the study. The surgeons were not allowed to see the patients during the period in which they were receiving oxygen in the recovery room. Consequently, the patients as well as the surgical team (including the investigators) were blinded to the category of study population.

We recorded relevant parameters that might influence wound infection, including medical history (particularly diabetes, hypertension, and ischemic heart disease), body mass index, smoking history, inflammatory bowel disease, and intraoperative variables such as basic hemodynamic data, urine output, core temperature, oxygen saturation, and relevant laboratory values.

Following resection of the inflamed appendix, the surgical wound in the right lower quadrant of the abdomen was meticulously irrigated and sutured with absorbable sutures. The skin was closed using metal clips (including cases of gangrenous appendicitis).

We have classified the results of the histopathological analysis of the resected specimen into 4 subgroups: normal appendix without inflammatory changes, acute appendicitis, phlegmonous appendicitis, and gangrenous appendicitis (with or without perforation and local peritonitis).

The primary end point was SSI within 14 days of surgery. The secondary end point was the duration of postoperative hospitalization.

SURGICAL SITE EVALUATION

During hospitalization, surgical wounds were evaluated daily by the residents and senior surgeons, all blinded to the F_{IO_2} assignment (0.30 or 0.80). After patient discharge, further wound evaluation was done at the surgical outpatient clinic by an experienced senior surgeon within 2 weeks after surgery; when necessary, additional visits were scheduled. Surgical site infection was evaluated clinically according to obvious signs and symptoms such as local induration and erythema, purulent discharge, and the need to explore the wound. Supportive results included increased white blood cell count, fever, radiological evidence of infectious collection, positive culture findings, and resolution of mild infectious findings following antibiotic treatment. We used the ASEPSIS (additional treatment, serous discharge, erythema, purulent discharge, separation of deep tissues, isolation of bacteria, and stay in hospital prolonged >14 days) system score to assess the degree of healing and infection of the surgical wound.[22-24] This scoring method is based on objective, scored, multidimensional parameters, where a greater linear change indicates a greater likelihood of SSI and healing disturbances.

STATISTICAL ANALYSIS

We used SPSS version 11.5 statistical software (SPSS Inc, Chicago, Illinois) to assist with data analysis. We used the χ^2 test

Table 1. Characteristics of the Study and Control Groups

Characteristic	Study Group (n=107)	Control Group (n=103)	*P* Value	Total (N=210)
Sex, No. (%)				
Male	80 (74.7)	73 (70.9)	.64[a]	152 (72.7)
Female	27 (25.2)	30 (29.1)		57 (27.3)
Age, y				
Mean (SD)	28.5 (12.3)	27.6 (10.8)	.60[b]	28.0 (11.5)
Range	15-71	15-56		15-71
Medical background, %				
IHD	4.6	1.3	.37[c]	3.1
Hypertension	9.2	5.3	.38[a]	7.4
Diabetes	0.0	1.3	.47[c]	0.6
Pulmonary disease	0.0	2.7	.22[c]	1.3
IBD	. . .	. . .	. . .	. . .
Clinical data on admission				
Body temperature, °C				
Mean (SD)	36.9 (0.53)	36.9 (0.55)	.77[b]	36.9 (0.54)
Range	36.0-38.9	36.0-39.0		36.0-39.0
Abdominal pain				
%	100.0	98.6	.47[c]	99.4
Duration of pain, d				
Mean (SD)	1.32 (0.87)	1.36 (1.19)	.78[b]	1.34 (1.03)
Range	1-3	1-10		1-10
Abdominal tenderness, %	98.8	100.0	>.99[c]	99.4
Abdominal rigidity, %	89.3	86.5	.63[a]	88.0
Preoperative analysis				
WBC count, /μL				
Mean (SD)	13 400 (3700)	13 370 (3600)	.95[b]	13 400 (3600)
Range	4900-22 600	5300-22 200		4900-22 600
Hemoglobin, mean (SD), g/dL	14.45 (1.50)	14.34 (1.34)	.63[b]	14.40 (1.40)
Creatinine, mean (SD), mg/dL	0.89 (0.15)	0.88 (0.13)	.71[b]	0.88 (1.40)
BUN, mean (SD), mg/dL	12.58 (4.5)	12.54 (5.6)	.96[b]	12.56 (5.0)
Preoperative imaging, %				
CT	29.1	23.6	.27[a]	26.6
US	35.3	50.7	.07[a]	42.3

Abbreviations: BUN, blood urea nitrogen; CT, computed tomography; IBD, inflammatory bowel disease; IHD, ischemic heart disease; US, ultrasonography; WBC, white blood cell; ellipses, not noted in medical background.

SI conversion factors: To convert WBC count to $\times 10^9$ per liter, multiply by 0.001; to convert hemoglobin to grams per liter, multiply by 10.0; to convert creatinine to micromoles per liter, multiply by 88.4; and to convert BUN to millimoles per liter, multiply by 0.357.

[a] By χ^2 test.

[b] By *t* test.

[c] By Fisher exact test.

to evaluate the trial groups, the variation in antibiotic treatment, the use of preoperative imaging modalities, and the comparison of operative findings. We used the *t* test to evaluate statistical significance regarding parameters such as age, clinical data obtained on patient admission, preoperative laboratory blood test results, duration of surgery, length of hospital stay, and various intraoperative variables including arterial blood gases. We found the independent *t* test to be statistically appropriate for evaluation of length of hospital stay (a parameter that is not normally distributed) owing to the large size of the study groups (central limit theorem). We used the Fisher exact test to compare the medical background between the trial groups, the intraoperative findings, SSI, and postoperative complications. We used the Wilcoxon rank sum test for comparison of ordinal data to evaluate wound healing according to the ASEPSIS score. $P < .05$ was considered statistically significant.

RESULTS

From November 1, 2006, to May 31, 2009, 590 patients underwent surgery for acute appendicitis. The laparoscopic approach was used in 171 cases, leaving 419 patients who underwent open appendectomy. Nonconsenting patients and those who were not medically suitable, together with anesthesiologists unfamiliar with the study protocol, led to additional exclusion of 209 patients from the study population. The remaining 210 patients were randomly divided between the study group (107 patients, FIO_2 of 0.80) and the control group (103 patients, FIO_2 of 0.30). The decision to conclude the study at this stage was made owing to recent major changes in professional personnel in the departments of surgery and anesthesiology (avoiding strict adherence to the protocol) and the impression that statistical results had already been obtained. There were no significant differences between the groups in sex, age, medical history, and clinical presentation (**Table 1**). Parameters such as smoking history, obesity, timing of perioperative antibiotic administration, and abdominal shaving (in the operating room) as well as laboratory results were similar in both groups. Intraoperative hemodynamic parameters and intraoperative findings were not statistically different either (**Table 2**). The recordings of partial pres-

Table 2. Data Related to Surgery

Measurement	Study Group (n=107)	Control Group (n=103)	*P* Value	Total (N=210)
Duration of operation, min				
Mean (SD)	33.04 (10.6)	32.75 (10.3)	.86[a]	32.91 (10.5)
Range	15-60	17-59		15-60
Intraoperative findings, No. (%)				
Normal appendix	4 (3.7)	5 (4.85)	.75[b]	9 (4.3)
Acute appendicitis	18 (16.8)	17 (16.5)	.58[c]	35 (16.7)
Phlegmonous appendicitis	63 (58.9)	60 (58.2)	.67[c]	123 (58.6)
Gangrenous appendicitis	22 (20.6)	21 (20.4)	.86[c]	43 (20.47)
Intraoperative hemodynamic findings				
MAP, mm Hg				
Mean (SD)	84.9 (9.6)	86.5 (8.2)	.37[a]	85.6 (8.9)
Range	61-105	68-100		
Pulse, mean (SD), beats/min	77.2 (11.33)	78.8 (13.96)	.23[a]	77.4 (13.10)
Intraoperative fluids, mL				
Mean (SD)	808.3 (257)	835.8 (234)	.49[a]	820.5 (247)
Range	400-1500	300-1000		300-1500
Intraoperative blood	. . .	. . .	. . .	. . .
Transesophageal temperature, °C				
Preoperative				
Mean (SD)	36.7 (0.6)	36.7 (0.4)	.71[a]	36.7 (0.5)
Range	35.8-39.1	36.0-37.9		35.8-39.1
Postoperative				
Mean (SD)	36.4 (0.6)	36.4 (0.5)	.49[a]	36.4 (0.5)
Range	35.5-38.9	35.8-38.1		35.5-38.9
Arterial blood gases				
During anesthesia, before starting surgery				
pH, mean (range)	7.41 (7.3-7.6)	7.40 (7.3-7.5)	.47[a]	
Po_2, mm Hg				
Mean (SD)	263.30 (87)	179.95 (78)	.001[a]	
Range	125-459	115-464		
Pco_2, mean (SD), mm Hg	38.80 (5.3)	41.34 (21.5)	.33[a]	
Bicarbonate, mean (SD), mEq/L	24.60 (2.2)	25.13 (4.4)	.38	
Oxygen saturation, mean (SD), %	99.32 (1.2)	99.12 (2.4)	.53[a]	
Base access, mean (SD), mEq/L	0.36 (1.9)	0.40 (2.4)	.40[a]	
During surgery, before wound closure				
Po_2, mean (SD), mm Hg	275.47 (95)	149.37 (48)	.001[a]	
During stay in recovery room				
Po_2, mean (SD), mm Hg	188.6 (73)	142.3 (65)	.02[a]	

Abbreviations: MAP, mean arterial pressure; Pco_2, partial pressure of carbon dioxide; Po_2, partial pressure of oxygen; ellipses, no supplemental blood units were needed.

SI conversion factors: To convert Po_2 to kilopascals, multiply by 0.133; to convert Pco_2 to kilopascals, multiply by 0.133; and to convert bicarbonate to millimoles per liter, multiply by 1.0.

[a] By *t* test.

[b] By Fisher exact test.

[c] By χ^2 test.

sure of oxygen in arterial blood were significantly higher in the study group (receiving supplemental oxygen) during the initial and late stages of surgery and during the stay in the recovery room, as expected (Table 2).

Six cases of SSI were recorded in our study group (5.6%) in comparison with 14 cases (13.6%) in the control group ($P=.04$) (**Table 3**). Among those 6 SSIs in the study group, 4 needed wound exploration; 8 of 14 SSIs in the control group needed wound exploration ($P>.99$). One SSI occurred in the subgroup of patients with phlegmonous appendicitis (among 63 patients) in the study group in comparison with 6 SSIs among 60 patients in the control group ($P=.049$). Concerning the subgroup of gangrenous appendicitis, 3 of 22 patients (13.6%) had SSI in the study group, contrasting with 8 of 21 patients (38.1%) in the control group ($P=.06$). Concerning the ASEPSIS score of wound healing, which specifies the type and grading of SSI, a significant difference was also recorded between the 2 subject populations ($P=.03$) (**Table 4**).

The mean hospital stay was significantly longer in the control group (2.92 days) compared with the study group (2.51 days) ($P=.01$) (Table 3).

COMMENT

We have demonstrated a statistically significantly decreased rate of SSI following administration of supplemental oxygen in patients undergoing surgery for acute appendicitis. In addition, the hospital stay was significantly shorter in the study group (receiving supplemen-

Table 3. Postoperative Sequelae and Wound Infection

Outcome	Study Group	Control Group	*P* Value	Total
Length of hospital stay, mean (SD), d	2.51 (0.88)	2.92 (1.51)	.01[a]	2.71 (1.25)
SSI, No. (%)				
Total	6/107 (5.6)	14/103 (13.6)	.04[b]	20/210 (9.52)
Normal appendix	0/4	0/5	>.99[b]	0/9
Acute appendicitis	2/18 (11.1)	0/17	.20[b]	2/35 (5.7)
Phlegmonous appendicitis	1/63 (1.6)	6/60 (10.0)	.049[b]	7/123 (5.7)
Gangrenous appendicitis	3/22 (13.6)	8/21 (38.1)	.06[b]	11/43 (25.6)

Abbreviation: SSI, surgical site infection.
[a] By *t* test.
[b] By Fisher exact test.

Table 4. ASEPSIS Score of Wound Healing

	No. (%)		
Wound Healing	Study Group (n=107)	Control Group (n=103)	Total (N=210)
ASEPSIS score[a]			
Satisfactory healing	101 (94.4)	89 (86.4)	190 (90.5)
Disturbance of healing	2 (1.8)	5 (4.9)	7 (3.3)
Minor wound infection	2 (1.8)	3 (2.9)	5 (2.4)
Moderate wound infection	2 (1.8)	5 (4.9)	7 (3.3)
Severe wound infection	0	1 (1.0)	1 (0.5)
Wound exploration[b]	4/6 (66.7)	8/14 (57.1)	

Abbreviation: ASEPSIS, additional treatment, serous discharge, erythema, purulent discharge, separation of deep tissues, isolation of bacteria, and stay in hospital prolonged more than 14 days.
[a] *P*=.047 for 2-sided Wilcoxon rank sum test for comparison of ordinal data and *P*=.03 for 1-sided Wilcoxon rank sum test for comparison of ordinal data.
[b] *P*>.99 by Fisher exact test.

tal oxygen), while the background parameters relating to laboratory results and clinical presentation as well as population characteristics were without significant difference between the 2 groups.

We used the ASEPSIS scoring method, which has many advantages in clinical trials and is considered to be an objective, reliable, and reproducible method of surgical wound assessment, making it applicable to all forms of surgery. It takes into account a large multidimensional number of easily made assessments for final classification.[22-24] This score allows assessment of clinical and economic consequences (as it also relies on the length of hospital stay and the use of antibiotics) and is applicable to clinical trials. However, it should be said that there are variations in estimated percentage of wound infection among the most common definitions of SSI.[25]

As noted earlier, the medical data concerning the influence of supplemental oxygen on SSI are controversial, and the reasons are most likely multifactorial.[12-21] The use of different SSI definitions may in part be responsible for such discrepancy.[25] Another aspect is the interplay of different factors that are needed 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.[26] Standard methods of postoperative care are also important factors.[19] Statistical consideration such as power calculation for sample size can also affect the data interpretation.[21] The most important factor, in our opinion, that explains the mixed literature is the heterogeneity of the different study populations, 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. Our study adds to the literature as it overcame the main factor responsible for the mixed data related to SSI.

Our study population is relatively homogeneous in contrast to the recently published randomized, controlled studies dealing with supplemental oxygen and SSI as it includes 1 type of operation (open appendectomy), a single diagnosis (acute appendicitis), and uniformity of the surgical wound, located in the right lower quadrant of the abdomen. Accordingly, we expect our results to offer a better indication regarding the effects of normobaric hyperoxia in clean-contaminated surgical operations.

Although in most cases SSI is graded as a minor postoperative complication according to the common severity classifications of postoperative complications, it may pose a significant clinical problem for the patient as well as for the community in general.[27] As it is common to leave the surgical wound wide open for delayed primary suture in cases of gangrenous appendicitis, our results (including a significant reduction of SSI in the subgroups of patients with phlegmonous and gangrenous appendicitis) indicate a preferable option of suturing the wound in such cases while pro-

viding supplemental oxygen, without significantly increasing SSI.

There are several rationalizations for the beneficial perioperative use of supplemental oxygen to reduce SSI. It is well known that the ability of the neutrophil to eradicate bacteria is mediated by its oxidative killing capabilities, depending on the creation of bactericidal superoxide radicals from molecular oxygen.[28,29] Consequently, it is expected that increased oxygen tension will lead to improved phagocytic activity and hence to reduced SSI.[12,13] In addition to augmentation of the bacteria-killing activity by leukocytes (which is impaired under a hypoxic atmosphere), hyperoxia also exerts direct bacteriostatic and bactericidal activity mostly on anaerobic bacteria. An additional explanation for SSI reduction is the role of oxygen in improving wound healing, mainly by facilitating crucial steps such as fibroblast proliferation, angiogenesis, and increased tissue perfusion.[30-32] In light of reduced oxygen tension in the surgical wound due to hemodynamic changes during anesthesia and the interruption of the blood supply by surgery itself, increasing tissue oxygen tension would be expected to ameliorate SSI.[28] On the other hand, hyperoxia may cause adverse reactions by increasing free radical content, potentially leading to oxidative stress and consequently resulting in cellular malfunction, DNA and protein injury, increased lipid peroxidation, and apoptosis.[15,33,34]

The involvement of oxygen in wound healing and tissue inflammation is even more complex as the inflammatory process is multifaceted. Especially relevant are the changes that occur in a relatively low-oxygen-tension environment (comparable to the surgical wound during surgery for an inflammatory process) in which the hypoxia-responsive transcription factor (hypoxia-inducible factor 1α [HIF-1α]) plays a major role.[35-37] The macrophages and neutrophils depend on HIF-1α for early inflammatory infiltration under a hypoxic atmosphere and for the regulation of anaerobic energy production by glycolysis.[36] Consequently, it may be deduced that supplemental oxygen exerts indirect effects on the inflammatory response by ameliorating tissue hypoxia, which serves as a key trigger of inflammation. Additionally, the hypoxic environment is left somehow unnecessary following resection of the inflammatory source (the appendix) together with effective antibiotic therapy. Another postulated mechanism for the beneficial aspects of hyperoxia combines it with reduced nitric oxide production.[37]

Recent studies have demonstrated a beneficial influence of hyperoxia by hyperbaric oxygen in diverse models of ischemia-reperfusion, protecting against oxidative stress.[32,38-40] The mechanism involves interference with several steps during proinflammatory processes following ischemia-reperfusion such as disturbances in polymorphonuclear leukocyte rolling and adherence to endothelial cells and the production of free radicals. Hyperoxia was also demonstrated to reduce the expression of endothelial adhesion molecules such as E-selectin and intercellular adhesion molecule 1 and to increase the production of superoxide dismutase and nitric oxide, subsequently leading to decreased oxidative stress and impaired polymorphonuclear leukocyte function.[41-43] All of these points exhibit direct inhibitory effects of oxygen on various steps of the inflammatory process, in addition to its indirect effect by reversing tissue hypoxia.[44,45]

The analogy of those recent studies dealing with supplemental oxygen to our study is not inclusive as most studies were done under hyperbaric oxygen, and the tissue oxygen tension should be considered to be higher. However, some of those prospective randomized trials done under normobaric hyperoxia support the beneficial influence of supplemental oxygen on SSI.[12-14]

The amount of physically dissolved oxygen in the blood increases in direct proportion to the ambient oxygen partial pressure, but to a lesser extent in comparison with the amount of dissolved oxygen under hyperbaric hyperoxia. However, it seems that such an increase is enough to provide its benefits to SSI. We may speculate that by increasing the amount of dissolved oxygen, the rate of postoperative SSI would be reduced even more; however, a prospective, randomized study is needed for validation of this.

In this context, an additional explanation of the reduced rate of SSI in our study group (with supplementary oxygen and room air) may stem from the avoidance of the adverse effects related to the use of nitrous oxide.[14]

One study limitation is the relatively small number of participants, although the major analyses have reached statistical significance. It should be mentioned that although the rate of SSI reached statistical significance ($P = .04$), using the 2-tailed Fisher exact test will lead to $P = .06$. Another point is the relatively lower-than-expected partial pressure of oxygen during the stay in the recovery room, maybe owing to less-than-optimal adherence by the anesthesiologists to the oxygen supplementation breathing protocol. As this is a double-blinded study, we did our best to reduce our active involvement during the stages of surgery to decrease bias. However, our results that point to a decreased rate of SSI even under moderate hyperoxia strengthen the argument in favor of the beneficial effects of supplemental oxygen on wound healing.

In conclusion, we have demonstrated that the use of supplemental oxygen is advantageous in operations for acute appendicitis. As this is the most common emergent operation in general surgery, decreasing the rate of SSI carries significant clinical and economic gains. In addition, as our study was conducted in a relatively homogeneous study population, our results support the beneficial effects of supplemental oxygen in clean-contaminated surgery in general.

Accepted for Publication: April 9, 2010.
Correspondence: Amitai Bickel, MD, Department of Surgery, Western Galilee Hospital, PO Box 21, Nahariya, Israel (amitai@netvision.net.il).
Author Contributions: *Study concept and design:* Bickel, Ivry, and Eitan. *Acquisition of data:* Bickel, Gurevits, and Vamos. *Analysis and interpretation of data:* Bickel and Ivry. *Drafting of the manuscript:* Bickel, Gurevits, Vamos, and Eitan. *Critical revision of the manuscript for important intellectual content:* Bickel and Ivry. *Statistical analysis:* Bickel. *Administrative, technical, and material support:*

Bickel, Gurevits, Vamos, and Ivry. *Study supervision:* Bickel, Gurevits, Ivry, and Eitan.
Financial Disclosure: None reported.

REFERENCES

1. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Am J Infect Control*. 1992;20(5):271-274.
2. Culver DH, Horan TC, Gaynes RP, et al; National Nosocomial Infections Surveillance System. Surgical wound infection rates by wound class, operative procedure, and patient risk index. *Am J Med*. 1991;91(3B):152S-157S.
3. Haley RW, Culver DH, Morgan WM, White JW, Emori TG, Hooton TM. Identifying patients at high risk of surgical wound infection: a simple multivariate index of patient susceptibility and wound contamination. *Am J Epidemiol*. 1985;121 (2):206-215.
4. Bremmelgaard A, Raahave D, Beier-Holgersen R, Pedersen JV, Andersen S, Sørensen AI. Computer-aided surveillance of surgical infections and identification of risk factors. *J Hosp Infect*. 1989;13(1):1-18.
5. Miles AA, Miles EM, Burke J. The value and duration of defence reactions of the skin to the primary lodgement of bacteria. *Br J Exp Pathol*. 1957;38(1):79-96.
6. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery*. 1961;50:161-168.
7. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med*. 1992;326(5):281-286.
8. Jonsson K, Jensen JA, Goodson WH III, West JM, Hunt TK. Assessment of perfusion in postoperative patients using tissue oxygen measurements. *Br J Surg*. 1987;74(4):263-267.
9. Hartmann M, Jönsson K, Zederfeldt B. Effect of tissue perfusion and oxygenation on accumulation of collagen in healing wounds: randomized study in patients after major abdominal operations. *Eur J Surg*. 1992;158(10):521-526.
10. Akça O, Melischek M, Scheck T, et al. Postoperative pain and subcutaneous oxygen tension. *Lancet*. 1999;354(9172):41-42.
11. Kurz A, Sessler DI, Lenhardt R; Study of Wound Infection and Temperature Group. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med*. 1996;334(19):1209-1215.
12. Greif R, Akça O, Horn EP, Kurz A, Sessler DI; Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med*. 2000;342(3):161-167.
13. Belda FJ, Aguilera L, García de la Asunción J, et al; Spanish Reduccion de la Tasa de Infeccion Quirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA*. 2005;294 (16):2035-2042.
14. Myles PS, Leslie K, Chan MTV, et al; ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology*. 2007;107(2):221-231.
15. Pryor KO, Fahey TJ III, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *JAMA*. 2004;291(1):79-87.
16. Mayzler O, Weksler N, Domchik S, Klein M, Mizrahi S, Gurman GM. Does supplemental perioperative oxygen administration reduce the incidence of wound infection in elective colorectal surgery? *Minerva Anestesiol*. 2005;71(1-2):21-25.
17. Gardella C, Goltra LB, Laschansky E, et al. High-concentration supplemental perioperative oxygen to reduce the incidence of postcesarean surgical site infection: a randomized controlled trial. *Obstet Gynecol*. 2008;112(3):545-552.
18. Meyhoff CS, Wetterslev J, Jorgensen LN, et al; PROXI Trial Group. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA*. 2009; 302(14):1543-1550.
19. Chura JC, Boyd A, Argenta PA. Surgical site infections and supplemental perioperative oxygen in colorectal surgery patients: a systematic review. *Surg Infect (Larchmt)*. 2007;8(4):455-461.
20. Al-Niaimi A, Safdar N. Supplemental perioperative oxygen for reducing surgical site infection: a meta-analysis. *J Eval Clin Pract*. 2009;15(2):360-365.
21. Qadan M, Akça O, Mahid SS, Hornung CA, Polk HC Jr. Perioperative supplemental oxygen therapy and surgical site infection: a meta-analysis of randomized controlled trials. *Arch Surg*. 2009;144(4):359-367.
22. Wilson AP, Treasure T, Sturridge MF, Grüneberg RN. A scoring method (ASEPSIS) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis. *Lancet*. 1986;1(8476):311-313.
23. Byrne DJ, Malek MM, Davey PG, Cuschieri A. Postoperative wound scoring. *Biomed Pharmacother*. 1989;43(9):669-673.
24. Wilson AP, Weavill C, Burridge J, Kelsey MC. The use of the wound scoring method 'ASEPSIS' in postoperative wound surveillance. *J Hosp Infect*. 1990;16(4): 297-309.
25. Wilson APR, Gibbons C, Reeves BC, et al. Surgical wound infection as a performance indicator: agreement of common definitions of wound infection in 4773 patients. *BMJ*. 2004;329(7468):720-724.
26. Hunt TK, Hopf HW. High inspired oxygen fraction and surgical site infection. *JAMA*. 2009;302(14):1588-1589.
27. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. *Ann Surg*. 2009;250(2):177-186.
28. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg*. 1997;132(9):997-1004.
29. Allen DB, Maguire JJ, Mahdavian M, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg*. 1997;132(9):991-996.
30. García-Botello SA, García-Granero E, Lillo R, López-Mozos F, Millán M, Lledó S. Randomized clinical trial to evaluate the effects of perioperative supplemental oxygen administration on the colorectal anastomosis. *Br J Surg*. 2006;93(6): 698-706.
31. Hamzaoğlu I, Karahasanoğlu T, Aydin S, et al. The effects of hyperbaric oxygen on normal and ischemic colon anastomoses. *Am J Surg*. 1998;176(5):458-461.
32. Bitterman H, Muth CM. Hyperbaric oxygen in systemic inflammatory response. *Intensive Care Med*. 2004;30(6):1011-1013.
33. Chabot F, Mitchell JA, Gutteridge JM, Evans TW. Reactive oxygen species in acute lung injury. *Eur Respir J*. 1998;11(3):745-757.
34. Klatt P, Lamas S. Regulation of protein function by S-glutathiolation in response to oxidative and nitrosative stress. *Eur J Biochem*. 2000;267(16):4928-4944.
35. Nathan C. Points of control in inflammation. *Nature*. 2002;420(6917):846-852.
36. Cramer T, Yamanishi Y, Clausen BE, et al. HIF-1α is essential for myeloid cell-mediated inflammation. *Cell*. 2003;112(5):645-657.
37. Nathan C. Immunology: oxygen and the inflammatory cell. *Nature*. 2003;422(6933): 675-676.
38. Buras J. Basic mechanisms of hyperbaric oxygen in the treatment of ischemia-reperfusion injury. *Int Anesthesiol Clin*. 2000;38(1):91-109.
39. Tjärnström J, Wikström T, Bagge U, Risberg B, Braide M. Effects of hyperbaric oxygen treatment on neutrophil activation and pulmonary sequestration in intestinal ischemia-reperfusion in rats. *Eur Surg Res*. 1999;31(2):147-154.
40. Zinchuk VV, Khodosovsky MN, Maslakov DA. Influence of different oxygen modes on the blood oxygen transport and prooxidant-antioxidant status during hepatic ischemia/reperfusion. *Physiol Res*. 2003;52(5):533-544.
41. Kaelin CM, Im MJ, Myers RA, Manson PN, Hoopes JE. The effects of hyperbaric oxygen on free flaps in rats. *Arch Surg*. 1990;125(5):607-609.
42. Sukhotnik I, Coran AG, Greenblatt R, et al. Effect of 100% oxygen on E-selectin expression, recruitment of neutrophils and enterocyte apoptosis following intestinal ischemia-reperfusion in a rat. *Pediatr Surg Int*. 2008;24(1):29-35.
43. Buras JA, Stahl GL, Svoboda KK, Reenstra WR. Hyperbaric oxygen downregulates ICAM-1 expression induced by hypoxia and hypoglycemia: the role of NOS. *Am J Physiol Cell Physiol*. 2000;278(2):C292-C302.
44. Bitterman H. Bench-to-bedside review: oxygen as a drug. *Crit Care*. 2009;13(1): 205-212.
45. Benson RM, Minter LM, Osborne BA, Granowitz EV. Hyperbaric oxygen inhibits stimulus-induced proinflammatory cytokine synthesis by human blood-derived monocyte-macrophages. *Clin Exp Immunol*. 2003;134(1):57-62.