Perioperative Supplemental Oxygen Therapy and Surgical Site Infection

A Meta-analysis of Randomized Controlled Trials

Motaz Qadan, MBChB, MRCS(Edin); Ozan Akça, MD; Suhal S. Mahid, MRCS, PhD; Carlton A. Hornung, MPH, PhD; Hiram C. Polk Jr, MD

Objective: To conduct a meta-analysis of randomized controlled trials in which high inspired oxygen concentrations were compared with standard concentrations to assess the effect on the development of surgical site infections (SSIs).

Data Sources: A systematic literature search was conducted using the MEDLINE, EMBASE, and Cochrane databases and included a manual search of references of original articles, poster presentations, and abstracts from major meetings (“gray” literature).

Study Selection: Twenty-one of 2167 articles met the inclusion criteria. Of these, 5 randomized controlled trials (3001 patients) assessed the effect of perioperative supplemental oxygen use on the SSI rate. Studies used a treatment-inspired oxygen concentration of 80%. Maximum follow-up was 30 days.

Data Extraction: Data were abstracted by 3 independent reviewers using a standardized data collection form. Relative risks were reported using a fixed-effects model. Results were subjected to publication bias testing and sensitivity analyses.

Data Synthesis: Infection rates were 12.0% in the control group and 9.0% in the hyperoxic group, with relative risk reduction of 25.3% (95% confidence interval [CI], 8.1%-40.1%) and absolute risk reduction of 3.0% (1.1%-5.3%). The overall risk ratio was 0.742 (95% CI, 0.599-0.919; P = .006). The benefit from increasing oxygen concentration was greater in colorectal-specific procedures, with a risk ratio of 0.556 (95% CI, 0.383-0.808; P = .002).

Conclusions: Perioperative supplemental oxygen therapy exerts a significant beneficial effect in the prevention of SSIs. We recommend its use along with maintenance of normothermia, meticulous glycemic control, and preservation of intravascular volume perioperatively in the prevention of SSIs.


Surgical Site Infection (SSI), a frequent complication of major surgery, is associated with significant attributable morbidity and mortality, prolonged hospital length of stay, and a high cost to the patient and the institution. In clean-contaminated and contaminated surgery, such as elective major colorectal surgery, the reported risk of SSI is high. Other data have suggested a doubling of the mortality rate, with an annual cost of $1.8 billion to the US health care system and £1 billion to the National Health Service in England. Data provided by the National Nosocomial Infections Surveillance (NNIS) System and other institutions suggest that these figures may be improving but will be under-reported. Determining the avoidable factors that affect SSI will allow us to improve outcomes after surgery.

Oxidative killing of pathogens by polymorphonuclear leukocytes is the primary mechanism of defense against surgical pathogens. Oxygen partial pressures and wound tissue oxygen tensions have been shown to correlate with oxidative killing and have been reported to predict SSI rates. As a result, several randomized controlled trials (RCTs) have been conducted to assess the benefit of perioperative supplemental oxygen therapy. Although results that support the use of supplemental oxygen have shown it to decrease SSIs in some studies, results have been inconsistent overall. The trials included varying population subsets with varying criteria for diagnosing SSI (clinical-only scoring systems vs clinical and microbiologic diagnosis); therefore, the role of perioperative hyperoxia has remained undetermined. We combine the

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results of all double-blind RCTs comparing the use of high inspired oxygen concentrations with standard concentrations to determine the efficacy of this treatment in preventing SSIs.

METHODS

SEARCH AND SELECTION CRITERIA
A search was conducted, without language restrictions, of the MEDLINE (January 1, 1966, to September 30, 2007), EMBASE, and Cochrane databases using the search engines PubMed, Ovid, and Google Scholar. The following Medical Subject Heading terms were used: infection, oxygen, hyperoxia, wound, and surgical. Boolean operators (“and,” “or,” and “not”) were used to narrow and widen the search. To increase the number of hits using the Ovid search engine, we used the “explode” and “related article” functions. Based on the title of the publication and its abstract, we either downloaded the full article or requested it through our library. We manually searched the references of original and review articles and evaluated symposia proceedings, poster presentations, and abstracts from major surgical and anesthetic meetings for a 10-year period (1998-2007) to locate unpublished material and to reduce the likelihood of publication bias. Finally, we reviewed the reference lists of articles obtained to complete the search. We subsequently developed inclusion and exclusion criteria and subjected filtered results to sensitivity analyses to quantitatively evaluate the heterogeneity of the findings.

INCLUSION AND EXCLUSION CRITERIA
Abstracts, full articles, and “gray” literature (nonconventional publications) that had passed the primary screening procedure were retrieved. These publications were then screened to include the following: human clinical RCTs, studies with 2 arms using high (treatment) and normal (control) inspired oxygen concentrations perioperatively, and single-center and multicenter worldwide trials. The following works were excluded: American Society of Anesthesiology class 5/SE and moribund patient populations, purely laparoscopic (non–hand-assisted) procedures, minor outpatient (day-case) surgery studies, pediatric and neonatal studies, hyperbaric ventilation studies, hypercapnia studies, obesity studies, and case-control studies, case reports, letters, comments, reviews, and abstracts with insufficient details to meet the inclusion criteria. The primary outcome analyzed was SSI diagnosed: (1) clinically (NNIS wound infection index); Centers for Disease Control and Prevention SENIC [Study on the Efficiency of Nosocomial Infection Control] wound infection index; ASEPSIS [additional treatment, the presence of serious discharge, erythema, purulent exudate, and separation of the deep tissues, the isolation of bacteria, and the duration of inpatient stay] score, and purulent discharge alone or any combination of clinical markers, such as skin induration, erythema, or pyrexia, (2) microbiologically (positive culture of pus specimen), or (3) both clinically and microbiologically.

The interval from the date of surgery in which the SSI diagnosis was captured was different in each study, ranging from 14 days to 1 month. Furthermore, the study by Pryor et al used a medical record review to identify SSI, thereby capturing this information retrospectively.

DATA EXTRACTION
Data were abstracted by 3 independent reviewers (M.Q., O.A., and S.S.M.) to meet predetermined inclusion and exclusion criteria. Data were abstracted using a standardized form and included first author, publication year, study type, study location, patient demographics, study quality (determined using the Jadad scale), type and duration of surgery, and number of cases and SSIs diagnosed. In the case of a discrepancy, a consensus decision was made.

STATISTICAL ANALYSIS
We stratified the outcome variable in response to control (30%) or treatment (80%) perioperative oxygen concentrations as infected or noninfected. Meta-analysis was performed according to the recommendations of the Cochrane collaboration. In every study, we calculated the risk ratio (RR) and 95% confidence interval (CI) for the primary outcome, SSI. Relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) were calculated to assess whether the overall RR was of clinical importance. The RRR represents the proportional reduction in SSIs between the hyperoxic and control participants in a trial. The ARR signifies the absolute difference in infection rates between the groups. The NNT is the reciprocal of the ARR and denotes the number of patients who would need to be treated to prevent 1 SSI.

The RRs were combined according to a fixed-effects model (the Mantel-Haenszel method) that assumes the presence of homogeneity between individual trials and following our own subjective analysis of the 5 studies, bearing in mind the low power of heterogeneity tests in small study samples. With this model, trials are considered to be samples from the same population of patients. In effect, the smaller trials are random samples from 1 large common trial.

SENSITIVITY ANALYSIS
Sensitivity analysis was undertaken to evaluate the effect of excluding noncolorectal studies, studies that used nitric oxide mixtures, and studies that may have caused significant skew on the overall data.

VALIDITY ASSESSMENT
Several strategies were adopted to assess the validity of this approach. The F index was used to measure heterogeneity between studies. F values lie between 0% and 100%. Increasing F values represent increasing heterogeneity. By convention, F values greater than 50% represent heterogeneity. We also constructed funnel plots to inspect for the presence of publication bias, followed by quantitative assessment of publication bias using the Egger regression test, which detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero. If the CI does not include zero, there is evidence of publication bias. Statistical significance was assigned at the P < .05 level where appropriate. Analyses were performed using Comprehensive Meta-Analysis V2.0 (Biostat Inc, Englewood, New Jersey).

RESULTS
The initial search yielded 2167 potentially relevant articles (Figure 1). Of these, 1993 articles, which included irrelevant material, editorials, reviews, and animal trials, were automatically excluded by limiting the search parameters. Of the 174 remaining articles, the abstracts were screened, and 153 were excluded because they incorporated critically ill or pediatric population subgroups or assessed the effect of hyperbaric or postoperative oxygen
therapy only. This left 21 articles, which were further scrutinized. After the exclusion of non–double-blind RCTs and other non–oxygen-related trials (hypcapnia and temperature studies), only 5 double-blind RCTs comparing low and high inspired oxygen concentrations perioperatively remained for meta-analysis (Table 1 and Table 2).10–14

STUDY CHARACTERISTICS

Five studies met the inclusion criteria,10–14 of which 3 were multicenter trials12–14 conducted across Europe and Australia. Two were single-center trials10,11 conducted in the United States and Israel. All of the studies were double blind, although concern was raised about one study’s blinding methods.11,25 All of the studies used 80%, or a mean of 80%,14 oxygen as the hypoxic concentration. Thirty percent oxygen was used as the control concentration in all but 1 study11, which used 35%. Most studies continued oxygen supplementation for 2 hours postoperatively, although 1 study12 continued oxygen supplementation for 6 hours after surgery, and another study13 continued treatment for variable intervals, depending on local protocols in its multiple centers. A nitrous oxide mixture was incorporated in 3 studies,10,11,14 either in the control group alone or more frequently in controls than in treatment patients. Three studies10,12,13 included only colorectal procedures. Laparoscopic procedures were included only if an additional incision was also made. Pathologic findings included inflammatory and neoplastic disease.

A potential confounding factor was the variable use of prophylactic antibiotics between studies. Prophylaxis for SSI was not controlled for in all of these studies. Although some studies standardized use between study groups,10,12,13 prophylaxis varied according to the surgeon’s preferences or institutional practice.11,14

A total of 3001 patients were pooled from individual trials, of whom 1494 were randomly assigned to receive higher inspired oxygen concentrations perioperatively. Crude infection rates were 12.0% in the control arm and 9.0% in the hypoxic arm. Hyperoxia resulted in an RRR of 25.3% (95% CI, 8.1%–40.1%) and ARR of 3.0% (1.1%–5.3%). The NNT was 33.0 (18.8–90.9). The overall RR was 0.742 (0.599–0.919; P = .006) (Figure 2).

SENSITIVITY ANALYSES

Sensitivity analyses were conducted to determine whether excluding studies that involved general surgical procedures, studies that used nitrous oxide, the opposing study, and the largest study had a significant effect on the overall strength and direction of the results (Figure 2).

Exclusion of Noncolorectal and Nitrous Oxide Studies

Three studies10,12,13 included only colorectal procedures. The other 2 studies included a larger variety of operations. Excluding the noncolorectal-specific studies on the basis that colorectal operations have a more uniform rate of SSI resulted in a lower RR of 0.556 (95% CI, 0.383–0.808; P = .002; I² = 0.00). When the 3 studies10,11,14 that used nitrous oxide, either exclusively or more frequently in the control group, were excluded, an RR of 0.551 (95% CI, 0.375–0.808; P = .002) resulted. I² = 0.00 after the exclusion.

Exclusion of Opposing and Largest Studies

Excluding the study by Pryor et al11 (used 35% inspired oxygen in controls) yielded an RR of 0.667 (95% CI, 0.533–0.835; P < .001; I² = 0.00). Excluding the largest study, an RR of 0.744 (95% CI, 0.534–1.037; P = .64; I² = 74.186) was observed.14

VALIDITY ASSESSMENT

We created a funnel plot using the log of the RR and the standard error of the log of the RR as the x- and y-axes, respectively (Figure 3). Clustering of studies in a narrow band of the y-axis indicates that the studies have nearly the same precision, whereas clustering with respect to the x-axis indicates that they are similar with respect to effect size. Not all of the high-quality studies fell within the 95% CI (the inverted funnel), suggesting variability with respect to precision and effect. The studies were not distributed equally along the y-axis in the plot, suggesting potential publication bias. However, this was not supported by quantitative assessment of publication bias: the Egger regression, P = .80 (−.534 to 6.37; 95% CI). Publication bias assessments, RRRs, ARRs, and NNTs for individual sensitivity analyses are available from the corresponding author.

COMMENT

Surgical site infection is a common preventable outcome that has been the focus of quality improvement initiatives in recent years.16 Factors such as antibiotic drug selection and timing of administration, maintenance of perioperative normothermia and normoglycemia, meticulous detail to surgical technique, and adequate postoperative pain control have been proved to reduce the infection rate.2,27–31 The effect of supplementary perioperative oxygen continues to be debated, with propo-
Abbreviations: AP, abdominoperineal; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; M, multicenter; S, single center; SSI, surgical site infection.

aThe control group received 30% inspired oxygen (the study by Pryor et al11 used 35% inspired oxygen in controls) and the treatment group received 80% inspired oxygen.

b3 = 1 (range, 0-5).

cExcludes patients with diabetes mellitus, malnourishment (albumin level <3.3 g/dL [to convert to grams per liter, multiply by 10]), leukopenia (white blood cell count <2.5 × 10^9 cells/L [to convert to ×10^9 per liter, multiply by .001]), recent significant weight loss, or immunosuppression (including human immunodeficiency virus).

nents and opponents firmly divided over the issue.32 A recent review by Chura et al33 addressed the results of 4 of the 5 studies included in the present review but excluded the largest study, by Myles et al34 (n = 2012), because the results were not yet available. It has been argued by some researchers that despite the benefit incurred from the use of hyperoxia to reduce the SSI rate, no additional benefit on other variables, such as length of stay12,13 and time to first feed and removal of staples,33 was seen. Other researchers35 have suggested that outcome defined by SSI rate alone is clinically significant.

When we combined the results of all of the RCTs performed, we observed that perioperative hyperoxia reduced the risk of SSI. The pooled RRR of 25.3%, the ARR of 3.0%, and the NNT of 33.0 were statistically significant findings, which confirmed the benefit of supplementary hyperoxia.

Hyperoxia can cause pulmonary absorption atelectasis35 and oxygen radical formation in lung microves-
sels.36-38 However, no significant increase in pulmonary complications was observed in the included trials. Furthermore, a recent RCT39 showed no significant increase in atelectasis rates after 80% vs 30% inspired oxygen use. It has been argued that pulmonary complications arise when the oxygen concentration is maintained at 100% rather than 80%.40,41

All major surgical wounds are prone to bacterial contamination and the development of SSI. However, colorectal operations pose a greater risk because clean-contaminated surgery involves intraoperative exposure to a significant bacterial load. Consequently, prediction scores such as the NNIS index, the Centers for Disease Control and Prevention SENIC index, and ASEPSIS scores account for a greater risk of infection with these procedures.16-18

On this basis, when colorectal studies are pooled, these findings are consistent with the prediction of Dellinger,42 which suggests a more significant benefit from the use of hyperoxia in colorectal surgery. The increased benefit may
be a result of excluding the study by Pryor et al.\textsuperscript{11} However, unless any detrimental adverse effects are confirmed in this type of procedure, we advocate the use of perioperative hyperoxia to reduce SSI in colorectal surgery.

Myles et al\textsuperscript{14} studied 2012 patients and incorporated nitrous oxide in the anesthetic mixture in 1 arm of the study only (70\% nitrous oxide with 30\% oxygen). Control patients were treated with an average of 80\% oxygen in nitrogen. There was no requirement in the study protocol to continue 80\% oxygen in the postoperative period, and the definition of SSI was specifically stated as “if associated with purulent discharge, with or without a positive microbial culture; or pathogenic organisms isolated from aseptically obtained microbial culture.”\textsuperscript{14,22-24} The authors\textsuperscript{14} concluded that hyperoxia or the absence of nitrous oxide significantly reduced the SSI rate. Nitrous oxide use results in irreversible inhibition of vitamin B\textsubscript{12}, which inhibits methionine synthase, folate metabolism, and DNA synthesis. This is the proposed mechanism by which immunodeficiency and impaired wound healing may result.\textsuperscript{15-16} However, in a recent multicenter RCT,\textsuperscript{16} 418 patients undergoing colonic resections lasting more than 2 hours were studied; one group received 65\% nitrous oxide in oxygen and the other group received the same amount of nitrogen in oxygen. Surgical site infection was the primary end point. Fifteen percent of patients developed wound infections in the nitrous oxide group compared with 20\% in the nitrous oxide–free group (P = .21). Furthermore, no difference was encountered in time to first feed, ASEPSIS healing score, and mortality. The authors concluded that there were no deleterious effects associated with use of the gas. Similarly, Pryor et al\textsuperscript{11} used nitrous oxide in a greater proportion of controls but did not demonstrate an increased SSI rate. In fact, infection rates were higher in the hyperoxic group, which received significantly less nitrous oxide. These findings suggest that the reduction in SSIs seen in the hyperoxic group in the study by Myles et al\textsuperscript{13} may have largely been due to hyperoxia alone.

Myles et al\textsuperscript{10} did not demonstrate a significant beneficial effect from using a high oxygen concentration with no nitrous oxide in their treatment arm, the relevance of which is limited because the sample size was very small, resulting in an underpowered study.

A sensitivity analysis excluding studies that used nitrous oxide still demonstrated benefit from the use of hyperoxia on the SSI rate in the remaining trials. Therefore, even if nitrous oxide use was a risk factor for SSI,
there was, nevertheless, a significant benefit that may be attributed to hyperoxia alone. This finding may, once again, be largely due to exclusion of the “negative” results of Pryor et al, although this study did not demonstrate an increase in SSIs due to nitrous oxide use. When the studies that did not use nitrous oxide were excluded, a marginal but nonsignificant benefit was seen on the SSI rate (RR, 0.849; 95% CI, 0.656-1.099; P = .06) (data available on request). This result means that the inclusion of nitrous oxide gas in this analysis did not demonstrate added benefit with hyperoxia because of the deleterious effects of nitrous oxide gas in the control arm. This further supports the previous statement that the reduction in the SSI rate may mostly be due to hyperoxia alone. Isolation of the benefit of hyperoxia from the potential deleterious effect of nitrous oxide is largely futile because high oxygen concentrations naturally exclude nitrous oxide mixtures.

The trial by Pryor et al was the subject of intense scrutiny, with critics noting that the authors intentionally included a variety of procedures and did not standardize study groups. Differences in intraoperative blood loss and postoperative fluid replacement varied significantly between the groups despite intravascular volume depletion having been implicated as an etiologic risk factor for wound infection. Furthermore, body mass index was significantly higher in hyperoxic individuals. A recent review of obesity showed a negative effect on SSI outcome in colorectal procedures. In addition, obesity significantly reduces wound oxygen tensions, thus underlining the primary defense mechanism of polymorphonuclear leukocyte oxidative killing. The trial by Pryor et al was truncated after the evaluation of 160 patients due to the increase in SSIs seen in the hyperoxic group and was described as an a priori stopping point. Whether a priori termination was the correct thing to do will continue to be debated. Caution must be advised when interpreting truncated RCTs because results may inaccurately overestimate the effect that resulted in cessation of the study and render the study underpowered. Belda et al subsequently provided power calculations for sample size and determined that Pryor et al would have required more than 500 patients to detect the smallest clinically significant increase in SSIs. Because 35% oxygen was used in controls, we justified a sensitivity analysis that excluded the study by Pryor et al. This analysis showed a significant benefit from the use of hyperoxia to reduce the SSI rate in the remaining homogenous trials.

When excluding the largest study from the analysis, a marginal, although statistically insignificant, benefit persisted from the use of hyperoxia on the SSI rate. The large population enrolled by Myles et al may have exerted some skew on the overall data, which concerns us because more patients were included by Myles et al than by all the other studies combined. This fact questions whether the largest study overwhelms the smaller ones, especially given the homogeneity that the large study sample may impose on the collection of smaller heterogeneous studies. A small proportion of patients enrolled by Myles et al in the “hyperoxic” group (n = 156) did not receive more than 51% oxygen. However, mean inspired oxygen in the group was 80%, and, therefore, results could be pooled with 80% hyperoxic treatment groups from other studies.

There are usually limitations in meta-analysis due to inherent differences between combined studies. Differences herein include variability in antibiotic drug prophylaxis, length of follow-up for SSI (14-30 days), continuation of postoperative oxygen supplementation, and risk stratification of patients based on recognized scoring systems, a factor that was not included in most studies (e.g., the NNIS risk index, which assigns 1 point for each of the following: contaminated wound, American


he prevention of SSIs is a goal of all surgeons. A variety of measures have been definitively identified to reduce SSIs, including perioperative antimicrobial drug prophylaxis (including proper antibiotic drug selection, dosage, timing, redosing, and discontinuation), an appropriate hair removal technique if necessary, appropriate skin preparation, maintenance of patient normothermia, and maintenance of euglycemia. These and other evidence-based recommendations were made in the 1999 Guideline for the Prevention of Surgical Site Infection.1

Despite excellent evidence supporting these interventions for SSI prevention, full compliance has not yet been achieved with implementation of these measures.2 The Surgical Infection Prevention Project,3,4 with a goal to decrease the morbidity and mortality associated with SSIs, documented that only 55.7% of Medicare patients received preoperative antimicrobial prophylaxis for SSI prevention within 1 hour of surgical incision.5 A national collaborative (44 hospitals) that initiated these proven SSI prevention practices documented a 27% reduction in SSIs.6

Should we add the provision of supplemental high fraction of inspired oxygen (FiO2) concentrations to all patients to further reduce SSIs? Qadan and colleagues performed an excellent systematic review of 5 RCTs in which high inspired oxygen concentrations were compared with standard concentrations to assess the effect on SSIs.

On careful review, several problems with the conduct of the 5 studies included in the meta-analysis warrant examination. First, the definition of SSI was not consistent. The Centers for Disease Control and Prevention SSI definition includes all SSIs within 30 days after the operation, and it is well known that the use of intervals less than this will significantly underreport SSIs by up to 25%. Third, the study by Pryor et al used a medical record review to identify SSIs, thereby capturing this information retrospectively. The study by Myles et al did not include SSI as a primary outcome measure (the primary end point was duration of hospital stay). Fourth, there was no assessment of the individual patient’s risk factors for SSI. Risk adjustment for SSI (ie, the NNIS risk index, which assigns 1 point for each of the following findings: contaminated wound, ASA class 3 or higher, and a surgical procedure that lasted longer than the NNIS-derived cutoff value for the duration of that procedure) was not performed in these studies. Fifth, there was no control of appropriate perioperative antibiotic prophylaxis. The timing, selection, and duration of antibiotic prophylaxis for SSI were not controlled for in these studies and may be a confounding variable. Sixth, there was variable provision of high FiO2 supplemental oxygen. For the study by Myles et al, the study protocol required 80% FiO2 only during general anesthesia intraoperatively. There was no requirement in the study protocol to continue 80% oxygen in the postoperative period, whereas the other 4 studies continued high FiO2 supplementation for 2 to 6 hours postoperatively.

Appropriate prophylactic antibiotics given at the right time, avoidance of shaving, and maintenance of normo-