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Supplemental perioperative oxygen for reducing surgical site infection: a meta-analysis

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Abstract

Objective To assess the efficacy of supplemental perioperative oxygenation for prevention of surgical site infection (SSI).
Data sources Computerized PUBMED and MEDLINE search supplemented by manual searches for relevant articles.
Study selection Randomized, controlled trials evaluating efficacy of supplemental perioperative oxygenation versus standard care for prevention of SSI in patients' undergoing colorectal surgery.
Data synthesis Data on incidence of SSI were abstracted as dichotomous variables. Pooled estimates of the relative risk (RR) and 95% confidence interval (CI) were obtained using the DerSimonian and Laird random effects model and the Mantel-Haenzel fixed effects model. Heterogeneity was assessed using the Cochran Q statistic and I^2.
Results Four randomized controlled trials met the inclusion criteria. Supplemental perioperative oxygenation resulted in a reduced incidence of SSI [RR 0.70 (95% CI 0.52–0.94), $P = 0.01$], using a fixed effects model. Using the more conservative random effects model, the point estimate was similar [RR 0.74 (95% CI 0.39–1.43), $P = 0.37$], but the results failed to achieve statistical significance. The I^2 test showed moderate heterogeneity.
Conclusions Our analysis showed that supplemental perioperative oxygenation is beneficial in preventing SSI in patients undergoing colorectal surgery. Because of heterogeneity in study design and patient population, additional randomized trials are needed to determine whether this confers benefit in all patient populations undergoing other types of surgery. Supplemental perioperative oxygenation is a low-cost intervention that we recommend be implemented in patients undergoing colorectal surgery pending the results of further studies. Further research is needed to determine whether or not supplemental hyperoxia may cause unanticipated adverse effects.

Introduction

An estimated 27 million surgical procedures are performed each year in the United States [1]. Infection is a major complication of surgical procedures, and among surgical patients, surgical site infection (SSI) is the most common nosocomial infection [2]. SSIs prolong hospitalization, increase the cost of care [3], and are associated with excess mortality [2,4].

Prevention of SSI is essential. Oxidative killing by neutrophils has been shown to represent a major defence against SSI [5]. Oxidative killing is enhanced by high oxygen tension in the tissues, which reduces the risk of SSI [6]. Perioperative supplemental oxygenation to increase oxygen partial pressures in tissues has been studied as a means to reduce SSI. Four randomized controlled trials have been undertaken which have yielded mixed results [7,8–10]; some have shown a considerable reduction in the incidence of SSI [7], while one found an increased risk of SSI in patients receiving supplemental oxygen [8].

We undertook a meta-analysis to systemically review the published randomized clinical trials, evaluating the use of perioperative supplemental oxygen to decrease the risk of SSI in patients undergoing colorectal surgery.

Methods

We performed a computerized search of PUBMED (including MEDLINE), Current Contents, CINAHL, DARE and the Cochrane Network from inception until 15 September 2007, using the following keywords: SSI, wound infection, post-operative wound complications, post-operative wound infection, cellulitis or post-operative abscess formation, in combination with oxygen supplementation, hyperoxygenation, hyperoxia or oxygen therapy. The help of a librarian was also sought to ensure a comprehensive search.

We repeated the search with the same keywords using Google search engine (http://www.google.com.ezproxy.library.wisc.edu). We reviewed National Institutes of Health web site listings of ongoing trials (http://www.clinicaltrials.gov), and contacted authorities in the field for identification of additional unpublished studies. Reference lists of articles were searched to identify additional articles. No language restrictions were placed on the search.

Articles were included in our review if they met the following criteria: randomized controlled trials that compared supplemental perioperative oxygen with placebo or standard care in patients undergoing colorectal surgery, and reported SSI as an outcome. We excluded case reports, review articles, letters and editorials. For studies that included patients undergoing other types of surgery, we abstracted data for only the patients undergoing colorectal surgery.

Both authors independently reviewed each report identified by the search strategy. Disagreements among abstracters were resolved by discussion.

Data abstraction and statistical analysis

Data were extracted using a standard form for each relevant study and included the total number of patients in the study, those randomized to supplemental perioperative oxygen and the comparator, details regarding the randomization scheme, concentration and method of administration of oxygen, patient population, duration and type of surgery, adverse effects of supplemental oxygen, method of diagnosis and incidence of SSI. Data on mortality and length of intensive care unit (ICU) stay were also extracted.

Data on incidence of SSI and mortality were abstracted as dichotomous variables. We used the patient as the unit of analysis for the incidence of SSI and mortality. Other outcomes of interest were ICU length of stay and, hospital length of stay. Whenever necessary, authors of included articles were contacted to obtain additional information required for the statistical analysis. Studies were classified based on whether or not intention-to-treat analysis was used. In all situations, we used the diagnostic criteria used by the authors for diagnosis of SSI.

Pooled estimates of the RR and 95% confidence interval (CI) were obtained using the DerSimonian and Laird random effects model and the Mantel-Haenzel fixed effects model. Heterogeneity was assessed using the Cochran Q statistic and I^2, [100% × (Q-d.f.)/Q], where Q is Cochran's Q statistic and d.f. is degrees of freedom [11]. Degrees of freedom are equal to k-1 where k is the number of studies. Negative values of I^2 are put equal to 0% so I^2 values can range between 0% and 100%. '0%' indicates no observed heterogeneity; larger values indicate increasing heterogeneity. Subgroup analyses were used to explore the reasons for heterogeneity. Publication bias was assessed using a funnel plot and Eggers statistical test [12,13]. All statistical analyses were performed using Stats Direct Software (2002, Cheshire, UK).

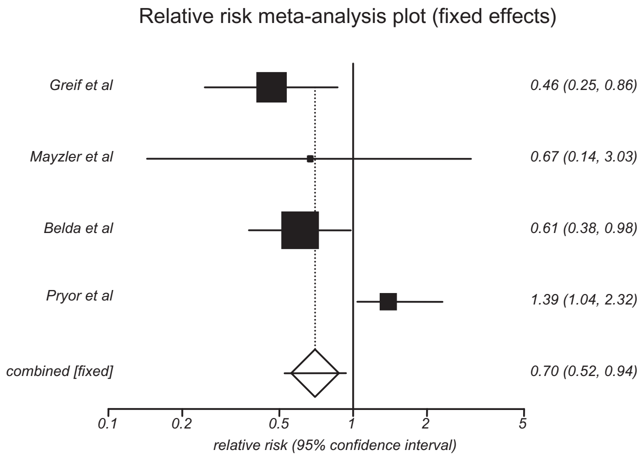

Figure 1 The relative risk of surgical site infection in studies using supplemental perioperative oxygen compared with standard care, using the fixed effects model.

Results

Study selection

The database search retrieved 30 citations of which four met our inclusion criteria (Fig. 1) [5–8]. Manual search did not identify additional trials that met inclusion criteria. The remaining studies fell into one or more of the following exclusionary categories: SSI not reported as an outcome (4) review article (15), editorial or letter (6). One trial was a randomized study of supplemental perioperative oxygen, and assessed clinical outcomes, including SSI but used a very low concentration of oxygen (28%) compared with room air [14]. This trial was, therefore, not included in our meta-analysis.

All studies were in the English language.

Study characteristics

The four trials enrolled 989 patients; 497 patients received perioperative supplemental oxygen, and 492 received standard care. Two of the four trials were multi-centre studies [7,10].

Greif *et al.* [7] studied 500 patients undergoing colorectal surgery; 250 patients were assigned to 80% oxygen, and 250 patients were given 30% oxygen. This study found that the SSI was 5.2% (13/250) in patients receiving 80% oxygen compared with 11.2% (28/250) in patients receiving 30% oxygen (RR 0.46, 95% CI 0.25–0.86).

Pryor *et al.* [8] included 160 patients, half received 80% oxygen and half received 30% oxygen. The study population included not only patients undergoing colorectal surgery but also other general surgical procedures. For our review, we included only the patients undergoing colorectal surgery (data obtained from study investigators), which amounted to 57 patients who received 80% oxygen and 51 patients who received 30% oxygen. SSI occurred in 14 of 57 patients (24.4%) in the 80% group and nine of 51 in the 30% oxygen group (RR 1.39, 95% CI 1.04–2.32). This is the only study that found a higher rate of SSI in patients receiving 80% Fio2.

Table 1 Characteristics of the studies included in our analysis

Author, year	Inclusion criteria	Definition of surgical site infection (SSI)	Duration of follow-up	Treatment	Comparator
Greif, 2000 [7]	age 18–80 years, elective colorectal resection*	Purulent drainage from surgical wound with positive microbiologic cultures According to AEPSIS scoring system†	15 days	80% oxygen	30% oxygen
Pryor, 2004 [8]	age over 18 years, colorectal surgery‡	(1) surgical team documentation of a clinical assessment of SSI; (2) change in management as a result of diagnosis, such as opening of wound, further surgery or aspiration; (3) at least three of the following criteria: leukocytosis >11 000 /μL^{-1}, temperature >38.5°C, radiological evidence of infection, extrusion of pus from the wound, positive culture result from infected site and resolution of wound erythema and induration after antibiotic therapy	2 weeks	80% oxygen	35% oxygen
Mayzler, 2005 [9]	elective colorectal surgery	Wound erythema with pain and purulence	4 weeks	80% oxygen	30% oxygen
Belda, 2005 [10]	age 18–80, elective colorectal resection*	Centers for Disease Control and Prevention criteria According to AEPSIS scoring system†	2 weeks	80% oxygen	35% oxygen

*Colorectal resection surgeries, mostly for cancer or inflammatory bowel disease, including an abdomino-perineal pull-though, minor colorectal surgeries are not included (e.g. polypoectomy or isolated colostomy).
†ASEPSIS score is derived from the weighted sum of points assigned for the following: duration of administration of antibiotics, drainage of pus during local anaesthesia, debridement of the wound during general anaesthesia, serous discharge, erythema, purulent exudates, separation of deep tissues, isolation of bacteria from the discharge, hospitalization for >14 days. Higher scores indicate poor healing and a greater likelihood of infection [28].
‡Including: hemicolectomy, sigmoidectomy, low anterior resection and abdomino-perineal resection. Fully laparoscopic surgeries are not eligible.

Mayzler *et al.* randomized 38 patients undergoing elective colorectal surgery for malignancy, 19 to an admixture of 80% oxygen and 20% nitrogen or 30% oxygen [9]. SSI was observed in two patients, receiving 80% oxygen and in three patients, receiving 30% oxygen. The investigators did not find statistically significant benefit in using supplemental perioperative oxygenation for reducing SSI (RR 0.67, 95% CI 0.14–3.03).

In their large, multi-centre study in Spain, Belda *et al.* [10] included 300 patients, of whom 291 were included in the analysis; 148 patients received 80% oxygen, and 143 patients received 30% oxygen. SSI occurred in 22/148 (15%) of patients, receiving 80% oxygen compared with 35/143 (24%) in patients, receiving 30% Fio2. (RR 0.61, 95% CI 0.38–0.98).

The characteristics of the four randomized controlled trials are summarized in Table 1.

Description of intervention

In three trials, supplemental perioperative oxygen was administered during surgery and for 2 hours after [7–9]. In Belda *et al.*, patients were assigned after induction of anaesthesia to oxygen/air mixture with a fraction of inspired oxygen of 30% or 80% for the duration of surgery and for the first six postoperative hours [10]. In all the trials, oxygen was administered using non-rebreathing face-masks with a reservoir.

Other measures for reducing the risk of SSI

Greif *et al.* used a mechanical bowel preparation without antibiotics. Prophylactic antibiotics were given before surgery and for a mean of 2.7 days following surgery [7]. Belda *et al.* used mechanical bowel preparation without antibiotics or antisepics. Metronidazole plus cefoxitin or a third generation cephalosporin were administered perioperatively, 60–90 minutes before the surgical incision and up to 48 hours after surgery [10]. Surgical wounds were covered with conventional gauze bandages. An antiseptic solution was applied on the surface of the surgical wound but no intraperitoneal antibiotics or antiseptics were instilled. Mayzler *et al.* used a bowel preparation regimen prior to surgery that included intraluminal antibiotics (vancomycin and erythromycin). Ampicillin, garamicin and metronidazole were administered 1 hour before surgery [9]. The duration of antibiotics after surgery was not specified in this study. Patients in the study by Pryor *et al.* also underwent a bowel preparation; data on whether or not intraluminal antibiotics were used were not reported [8].

Perioperative normothermia was used in three trials [7,9,10], and was not mentioned in one.

Details of randomization and study design

Details of randomization were provided in all four trials. Greif *et al.* [7] and Belda *et al.* [10] used computer generated random codes; Pryor *et al.* [8] and Mayzler *et al.* [9] used a random number table.

Allocation concealment was reported in three trials, using sealed sequentially numbered envelopes [7,8,10]. Blinding was reported in all four studies; the trials by Greif *et al.* [7], Pryor *et al.* [8] and Belda *et al.* [10] were double-blinded, and in the study by Mayzler *et al.*, the surgeons evaluating for the outcome measure of SSI were unaware of the patients group assignment [9].

Table 2 Incidence of surgical site infection in randomized controlled trials of supplemental perioperative oxygen administration

Author	Number of patients receiving 80% oxygen	Number (%) of patients with surgical site infection (SSI) receiving 80% oxygen	Number of patients receiving 30% oxygen	Number (%) of patients with SSI receiving 30% oxygen
Greif *et al.* [7]	250	13 (5.2%)	250	28 (11.2%)
Pryor *et al.* [8]	57	14 (24.5%)	51	9 (17.6%)
Mayzler *et al.* [9]	19	2 (10.5%)	19	3 (15.7%)
Belda *et al.* [10]	148	22 (14.9%)	143	35 (24.4%)

Loss to follow-up was reported in three trials. Three patients withdrew in the study by Greif *et al.* (0.5%), and were assumed to be uninfected. Pryor *et al.* reported that in the group assigned to 80% Fio2, 5 of 85 (6%) patients were excluded because of a change in surgery or the anaesthesiologist. In both these trials [7,8], however, intention to treat analysis was used. In the study by Belda *et al.*, nine of 300 patients were lost to follow-up, and 291 patients were included in the final analysis [10].

Definition of SSI

The authors used various definitions of SSI in their studies. In the study by Belda *et al.* [10], surgical wounds were assessed daily for infection by surgeons who were unaware of patients treatment groups. Definitions from the Centers for Diseaes Control and Prevention were used for the diagnosis of SSI [2]. Only infections diagnosed in the first 2 weeks following surgery were included. Mayzler *et al.* reported a follow-up period of 4 weeks. The investigators defined wound infection as the appearance of erythema with pain and drainage of fluid or purulent secretions [7]. Greif *et al.* defined infection as purulent discharge from the wound with positive microbiologic cultures [7]. The ASEPSIS score was also used to determine the likelihood of infection and wound healing. Pryor *et al.* used the following criteria to define an SSI: (1) surgical team documentation of a clinical assessment of SSI; (2) change in management as a result of diagnosis, such as opening of wound, further surgery or aspiration; and (3) at least three of the following criteria: leukocytosis >11 000 μL^{-1}, temperature >38.5°C, radiological evidence of infection, extrusion of pus from the wound, positive culture result from infected site and resolution of wound erythema and induration after antibiotic therapy [8].

Incidence of SSI

Overall, two studies found a statistically significant reduction in SSI in patients undergoing colorectal surgery who received 80% perioperative oxygen [7,10]. One study did not find a statistically significant difference in SSI in patients receiving perioperative oxygen [9], and in one trial, rates of SSI were higher in the group that received 80% oxygen [8] (Table 2).

Supplemental perioperative oxygenation resulted in a reduced incidence of SSI [RR 0.70 (95% CI 0.52–0.94), $P = 0.01$], using a fixed effects model (Fig. 1). Using the more conservative random effects model, the point estimate was similar [RR 0.74 (95% CI 0.39–1.43), $P = 0.37$] (Fig. 2), but the results failed to achieve statistical significance. The I^2 test showed moderate heterogeneity.

Secondary outcomes

Three trials included in our analysis reported data on a number of secondary outcomes, including wound healing characteristics,

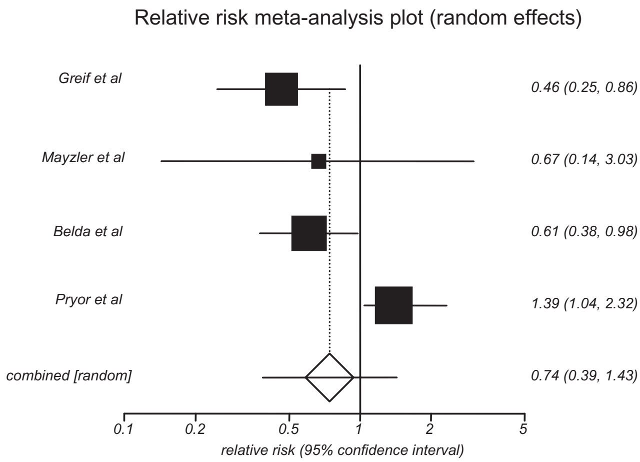

Figure 2 The relative risk of surgical site infection in studies using supplemental perioperative oxygen compared with standard care, using the random effects model.

ICU admission, return of bowel function, solid food intake, walking, removal of staples and hospitalization after surgery. Greif *et al.* reported lower ASEPSIS (Additional treatment, Serous discharge, erythema, Purulent exudates, separation of deep tissues, isolation of bacteria and duration of inpatient stay) scores in patients receiving 80% oxygen (mean score three compared with five in patients receiving 30% oxygen), $P = 0.01$ [7]. Belda *et al.* also found that although not statistically significant, fewer patients in the 80% oxygen treatment group had poor wound healing characteristics, as measured by the ASEPSIS score [10]. No differences in duration of hospitalization were found in any of the three studies. Mayzler did not report secondary outcomes [9].

Mortality

Two trials reported data on mortality. No statistically significant differences were seen in either study. In the study by Greif *et al.*, 1/250 in the 80% oxygen group died compared with 6/250 in the 30% oxygen group [7]. Pryor *et al.* reported mortality for the entire study population, not the subset that we included. No patients who received 80% Fio2 died, and one who received 30% Fio2 died [8].

Publication bias

Given the small number of studies that met our inclusion criteria, publication bias was of concern. Publication bias was assessed

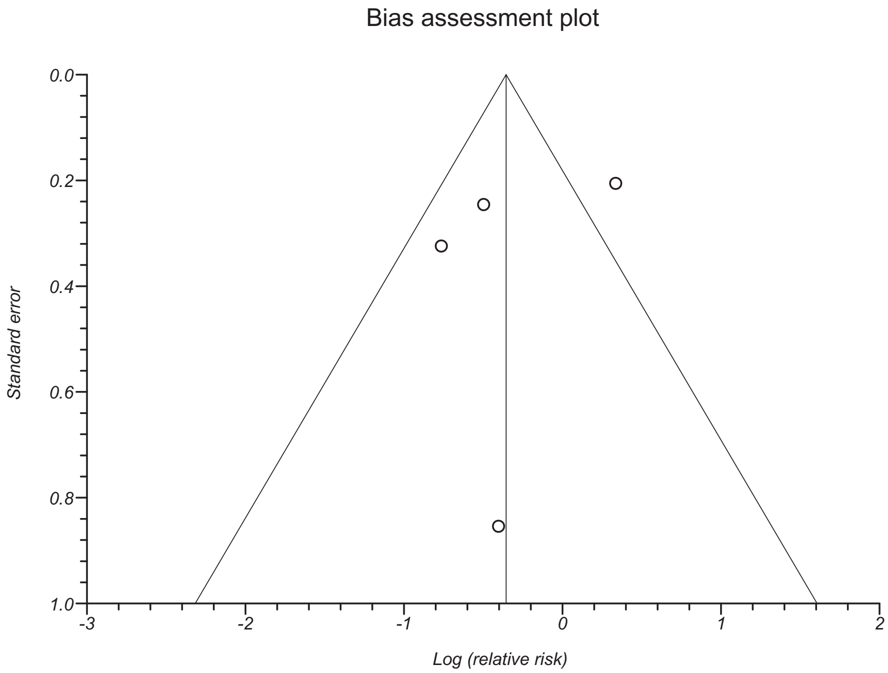

Figure 3 Funnel plot for assessment of publication bias. The shape of the funnel plot is asymmetrical indicating publication bias.

using a funnel plot and Eggers test (Fig. 3). The shape of the funnel plot was asymmetrical indicating publication bias although Eggers test was not statistically significant ($P = 0.56$).

Assessment of heterogeneity

We attempted to minimize heterogeneity in our analysis by including similar patient populations. However, our analysis showed substantial clinical heterogeneity, with I^2 value of 77%. The study by Pryor *et al.* accounted for all the heterogeneity, when this study was removed from the analysis to gauge its effect on the observed heterogeneity, the results showed a 50% relative risk reduction in the group receiving 80% oxygen (RR 0.55, 95% CI 0.38-0.80) [8].

Discussion

Surgical site infection is a major complication of abdominal surgery, associated with prolonged hospitalization, increased costs and excess mortality [15]. In recent years, randomized trials have identified a number of preventive measures that can substantially reduce the risk of SSI [2]. These include appropriate perioperative antibiotic prophylaxis [2], maintenance of perioperative normothermia [16] and control of hyperglycaemia [17,18].

Achieving high oxygen tension at the site of surgery has been proposed as a means of reducing the risk of SSI, based on data that oxygen can enhance the oxidative processes in white cells, thus facilitating bacterial killing [6]. A number of preclinical studies have shown that provision of high tissue oxygen concentrations promotes local wound healing in animal models [19,20]. Recent studies in humans have found that administration of supplemental oxygen in the perioperative period to patients undergoing colorectal surgery may reduce the risk of SSI [7,9,10,21]. However, not all studies have found this benefit, and one paradoxically found an increased risk of SSI with supplemental perioperative oxygenation administration [8]. Recent evidence-based reviews and editorials have recommended the use of supplemental perioperative oxygenation for prevention of SSI [22,23], but no meta-analysis has systematically quantified the magnitude of the effect.

Our analysis combining the results of four randomized controlled trials shows that supplemental perioperative oxygenation is associated with a 30% relative reduction in the risk of SSI. Although the statistical significance was retained only in the fixed effects model and not in the random effects model, the point estimates were very similar for both analyses. The random effects model provides a more conservative estimate of the 95% CI, taking heterogeneity into account.

We attempted to minimize heterogeneity in the included studies by including only patients that were undergoing colorectal surgery from the study by Pryor *et al.* as all the other trials included only patients undergoing colorectal surgery. In contrast to the positive results found in the two larger studies of perioperative supplemental oxygen, Pryor *et al.* found that administration of 80% oxygen conferred a greater risk of SSI. This increased risk was also found for the subgroup of patients undergoing colorectal surgery [8].

A number of possible explanations have been put forth to account for the disparate results in the study by Pryor *et al.*, including the heterogeneity of the study population and lack of standardization of perioperative procedures [22]; these cannot entirely explain why the study population receiving 80% supplemental oxygen would have a higher risk of infection. When the study by Pryor was excluded from the analysis, not surprisingly, the relative risk reduction with supplemental perioperative oxygen was even greater at 50%.

Adverse effects of 80% oxygen administration were not explicity addressed in the published clinical trials included in our meta-analysis. The use of 100% oxygen has been found to cause atelectasis [24]. This has not been shown with the 80% concentrations used by the studies in our analysis. It has been suggested that dose-response assessments should be undertaken to determine the lowest possible concentration of oxygen that will reduce the risk of SSI while posing minimum risk for harm [25]. A recent review of the effects of perioperative oxygenation, including potential adverse effects, has been published [26].

Recent studies have suggested that mild hypercapnia may enhance tissue oxygen tension, even in patients receiving supplemental oxygen, thus further reducing the risk of infection [27]. This hypothesis has not yet been tested in a clinical trial.

The main limitation of our meta-analysis is the heterogeneity stemming from the design of the original studies. Differing definitions of SSI, patient populations, surgical practices and duration of perioperative oxygen used may have contributed to the heterogeneity.

The disparate results from the study by Pryor *et al.* [8] suggest that further research is necessary to determine the utility of routinely using 80% oxygen for all types of abdominal surgery. However, as the bulk of the evidence points towards a benefit, and this is a low-cost, low-risk intervention, we recommend the use of 80% supplemental perioperative oxygen to reduce the risk of SSI in patients undergoing colorectal surgery. However, careful monitoring of SSI rates is essential to allow prompt detection of an increased incidence of SSI. Future studies should also undertake formal cost–effectiveness analyses to allow optimal allocation of already constrained resources for infection control.

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