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Review Article

REVIEW ARTICLE

Effect of intraoperative hyperoxia on the incidence of surgical site infections: a meta-analysis

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Abstract

Background: Whether supplemental intraoperative oxygen reduces surgical site infections remains unclear. Recent recommendations from the World Health Organization and Center for Disease Control to routinely use high inspired oxygen concentrations to reduce infection risk have been widely criticized. We therefore performed a meta-analysis to evaluate the influence of inspired oxygen on infection risk, including a recent large trial.

Methods: A systematic literature search was performed. Primary analysis included all eligible trials. Sensitivity analyses distinguished studies of colorectal and non-colorectal surgeries, and excluded studies with high risk of bias. Another post-hoc sensitivity analysis excluded studies from one author that appear questionable.

Results: The primary analysis included 26 trials (N=14,710). The RR [95%CI] for wound infection was 0.81 [0.70, 0.94] in the high vs. low inspired oxygen groups. The effect remained significant in colorectal patients (N=10,469), 0.79 [0.66, 0.96], but not in other patients (N=4,241), 0.86 [0.69, 1.09]. When restricting the analysis to studies with low risk of bias, either by strict inclusion criteria (N=5,047) or by researchers' judgment (N=12,547), no significant benefit remained: 0.84 [0.67, 1.06] and 0.89 [0.76, 1.05], respectively.

Conclusions: When considering all available data, intraoperative hyperoxia reduced wound infection incidence. However, no significant benefit remained when analysis was restricted to objective- or investigator-identified low-bias studies, although those analyses were not as well-powered. Meta-analysis of the most reliable studies does not suggest that supplemental oxygen substantively reduces wound infection risk, but more research is needed to fully answer this question.

Keywords: anaesthesia; hyperoxia; meta-analysis; surgical wound infection

All surgical wounds become contaminated, but effective host defences usually prevent contamination from progressing to clinical infection. The most important defence again bacterial contamination is oxidative killing by neutrophils.[1,2] Killing

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Editor's key points

- Whether supplemental intraoperative oxygen reduces surgical site infections remains unclear, despite recent publication of a very large trial.
- The authors conducted a meta-analysis of relevant trials, including sensitivity analyses restricted to higher-quality trials.
- The primary analysis included more than 14 000 subjects, and indicated that the relative risk for wound infection was 0.70–0.94 (95% confidence interval, high *vs* low inspired oxygen groups). However, when analysis was restricted to studies with low risk of bias no significant benefit remained.

requires molecular oxygen and depends on tissue oxygen over the observed clinical range.[3] The easiest way to increase tissue oxygenation is to augment inspired oxygen. For example, intraoperative tissue oxygen partial pressure is typically about 6.6 kPa in patients given 30% inspired oxygen and about 13.3 kPa in those given 80% inspired oxygen.[3]

Given the importance of tissue oxygen, it was unsurprising that the first two major trials reported that supplemental oxygen halves the risk of surgical site infection (SSI).[4,5] However, many subsequent trials, including the largest,[6,7] report that oxygen does not reduce infection risk. Whether supplemental oxygen, which is inexpensive and easy to provide, reduces infection risk, thus remains in dispute. Consistent with heterogeneous underlying reports, recent meta-analyses conflict, with some emphasising a possible beneficial effect of high inspired oxygen fraction (FiO_2) on SSI[8] while others emphasise possible detrimental effects.[9]

Despite obvious uncertainty, the World Health Organization recently published recommendations for the prevention of SSI that include use of inspired FiO_2 of 0.8 during surgery, and when possible for several hours thereafter.[10] This recommendation was apparently largely based a meta-analysis that omitted a recent 560 patient randomised trial that reported no benefit from supplemental oxygen.[7] The World Health Organization recommendation was widely criticised.[11–14] Curiously, the US Centers for Disease Control recently promulgated similar guidelines[15] despite divergent trial results and lack of general consensus.

In a recent, alternating-intervention trial, we assigned more than 5700 colorectal patients to 30% or 80% intraoperative inspired oxygen.[16] Supplemental oxygen did not reduce the primary composite of deep- and organ-space infection and major healing-related complications. Our recent trial is by far the largest. It is thus of considerable interest to include these new data in a meta-analysis of supplemental oxygen and SSI in adults having non-cardiac surgery. Secondarily, we evaluated the influence of intraoperative FiO_2 on SSI in patients having colorectal surgery and when analysis was restricted to higher-reliability trials.

Methods

We performed a systematic literature review and meta-analysis of trials in which investigators assigned patients to high or low intraoperative inspired oxygen and assessed SSIs. The last Cochrane meta-analysis was published in 2015.[9] We used similar searching rules, as detailed in the Appendix. As the Cochrane review was based on a search concluded in February 2014, we limited our search to studies published since January 2014. Our last search date was January 11, 2017. To those results, we added our recent alternating intervention trial.[16]

Eligibility criteria

After performing the preliminary search, two authors (B.C and Y.N.S) independently reviewed the search results for studies fulfilling all the following criteria:

(i) randomised clinical trial;
(ii) adults aged 18 yr or older;
(iii) elective or urgent surgeries with general or neuraxial anaesthesia;
(iv) comparison of high $FiO_2 \geq 60\%$ to low $FiO_2 \leq 40\%$ with a high/low FiO_2 ratio ≥ 2;
(v) designated FiO_2 maintained intraoperatively, with or without postoperative oxygen manipulation;
(vi) SSI reported as an outcome.

Disputes about qualification for inclusion were adjudicated by a third investigator (D.I.S.). Blinding was not required and we considered any language. Results presented only as abstracts or in conference proceedings were included.

Data sources

Our search included the electronic databases Medline, Embase, Central, Cinahl, Web of science, and Google scholar and relevant articles' reference lists and the investigators' personal reference collections. We were not able to search the Chinese Biomedical Literature Database and the Latin American Caribbean Health Sciences Literature (LILACS). Our main search strategies relied on the previous meta-analysis by Wetterslev and colleagues[9] extended from January 2014 to January 2017 and are detailed in the Appendix.

Extracted data included the number of participants and their demographic characteristics along with the type of surgery. We also recorded intervention details including the FiO_2 in each group, use of N_2O, continuation of the intervention into the postoperative period, and duration of anaesthesia. We considered study methodology including randomisation method, allocation concealment, blinding, completeness of primary outcome availability and reporting, and how SSIs were defined. Finally, we evaluated statistical methodology including appropriate sample size calculations and sufficient power, the number of patients included in analysis, and whether analysis was conducted on an intension-to-treat basis.

Eligible trials were evaluated for methodological strength according to *a priori* domains based on the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[17] Each domain was ranked as having low, unclear, or high risk of bias. Then, an overall risk of bias was evaluated as low or high using two distinct approaches: first, using strict criteria according to which any single domain rated as having either high or unclear risk of bias was sufficient to rank the study as having an overall high risk of bias. Second, using the investigators' clinical judgment and perception of the potential effect of every domain on each study's actual risk of bias. This process was independently performed by two investigators (B.C and Y.N.S). Interevaluator discrepancies were adjudicated by another investigator (D.I.S).