

CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 36

Effect of high perioperative oxygen fraction on surgical site infection

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The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”¹ The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

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1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

SELECTED ARTICLE

Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009;302:1543-50.

ABSTRACT

Objective: To assess whether using 80% oxygen reduces the frequency of surgical site infections (SSIs) without increasing the frequency of pulmonary complications in patients undergoing abdominal surgery. **Design:** Multicentre randomized controlled trial. **Setting:** Fourteen Danish hospitals. **Patients:** Fourteen hundred patients who underwent abdominal surgery were accrued between October 2006 and October 2008. **Intervention:** Patients were randomly assigned to receive either 80% or 30% oxygen during and for 2 hours after surgery. **Main outcome measures:** Surgical site infection within 14 days of surgery, defined according to the criteria of the Centers for Disease Control and Prevention (CDC). Secondary outcomes included atelectasis, pneumonia, respiratory failure and mortality. **Results:** Surgical site infections occurred in 131 of 685 patients (19.1%) assigned to 80% oxygen versus 141 of 701 (20.1%) patients assigned to 30% oxygen (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.72–1.22, $p = 0.64$). Atelectasis occurred in 54 of 685 patients (7.9%) assigned to receive 80% oxygen versus 50 of 701 (7.1%) assigned to receive 30% oxygen (OR 1.00, 95% CI 0.75–1.66, $p = 0.60$); pneumonia occurred in 41 (6.0%) versus 44 (6.3%) patients, respectively (OR 0.95, 95% CI 0.61–1.48, $p = 0.82$); respiratory failure occurred in 38 (5.5%) versus 31 (4.4%) patients, respectively (OR 1.27, 95% CI 0.78–2.07, $p = 0.34$); and mortality within 30 days in 30 (4.4%) versus 20 (2.9%) patients, respectively (OR 1.56, 95% CI 0.88–2.77, $p = 0.13$). **Conclusion:** Using 80% oxygen versus 30% oxygen did not result in a difference in the rate of SSIs after abdominal surgery.

COMMENTARY

Improving postoperative outcomes and reducing lengths of stay in hospital are critical objectives driving perioperative medicine, which have resulted in the implementation of surgical safety checklists, precise definitions of postoperative outcomes and the use of evidence-based clinical care pathways.^{1,2} Although benefits will likely derive from entire clinical care pathways, including preoperative, intraoperative and postoperative care, the individual components of such pathways require evaluation of their individual merits to remain valid. Hyperoxia in this context refers to the provision of supplemental oxygen to patients in the perioperative phase in an attempt to reduce SSIs

and associated sepsis, which continues despite the timely use of antibiotics and careful adherence to strict protocols that ensure avoidance of hypothermia, hypovolemia and postoperative pain. The hypothesis behind providing oxygen concentrations (up to 80%) is that this may enhance early innate immune processes that require oxygen as a substrate for effective elimination of contaminating pathogens during surgery, such as reactive oxygen species formation and intracellular killing.

The study by Meyhoff and colleagues³ addressed the clinical question of whether using hyperoxia, delivered as an 80% perioperative fraction of inhaled oxygen, reduces the frequency of SSIs without increasing the frequency of pulmonary complications in patients undergoing abdominal surgery, as compared with patients receiving a 30% perioperative oxygen fraction. Whereas 2 previous clinical studies suggested a significant benefit from the use of hyperoxia in the perioperative setting,^{4,5} 3 further trials provided conflicting results,⁶⁻⁸ so a large randomized controlled trial was timely.

Overall this was a well designed, large trial with a number of methodologic strengths. It was a patient- and observer-blinded, randomized, multicentre controlled trial of an intervention that is feasible and relatively inexpensive in almost any setting. The methods of blinding, which were excellent and continued throughout the trial, set a standard for most investigators to try to emulate. The initial assignment to treatment was by computer-generated randomization using a central interactive voice-response system, stratified by centre, diabetes mellitus, acute or elective operations and body mass index. The authors went to further lengths to maintain blinding of the patients, clinicians and study personnel: anesthesia machines and oxygen flowmeters were covered, oxygen therapy was dually and separately charted and neither the ward staff nor the patients were informed of the group assignment. Further, the authors and statisticians went to the remarkable length of analyzing the data blinded and writing 2 versions of the manuscript: one based on the assumption that treatment group A received FiO_2 80% and group B received FiO_2 30% and the other based on the reverse assumption. Finally, they accounted for all 1400 patients who were randomly assigned to either group and reported on all of them, with none lost to follow-up.

Overall, the authors wisely investigated side effects of treatment and reported no major differences between the groups in either their characteristics or their relevant clinical outcomes, suggesting that whereas there were no detrimental side effects associated with the use of 80% oxygen concentrations, there were also no demonstrable benefits. The reported treatment effect of the primary outcome measure, SSIs within 14 days of surgery, was an OR of 0.94 in patients administered an FiO_2 of 80%, with a reported CI of 0.72–1.22. They also reported on a number of secondary outcomes, such as pneumonia, atelectasis,

respiratory failure, duration of postoperative hospital admission, admission to the intensive care unit, abdominal reoperation and mortality, for which there were no statistically significant differences. Although not powered to detect a difference in mortality, the reported difference in 30-day mortality favoured the FiO₂ 30% group (4.4% FiO₂ 80% v. 2.9% FiO₂ 30%; OR 1.56, 95% CI 0.88–2.77).

A further methodologic strength of the study was that both the intention-to-treat and the per-protocol analyses of the primary outcome were in agreement. For example, there were 51 patients randomly assigned to the 30% FiO₂ group who required a higher FiO₂ for more than 1 hour to maintain an adequate PaO₂. Presumably this group represented a potentially “contaminating” effect on the study. However, whether analyzed according to an intention-to-treat or an adherence to protocol methodology, the results remained the same: namely that in this particular patient population that included both elective and emergent surgeries and a wide range of abdominal surgical procedures, there was no compelling reason to increase the inspired oxygen concentration to reduce the rate of SSIs.

With an adjusted OR of 0.91 for SSIs with 95% CIs ranging from 0.69 to 1.20, this implies that the chance of SSIs developing could be reduced to 0.69 with an FIO₂ of 80% or, alternatively, could be 1.2 times more likely. In absolute terms, the difference in the rate of SSIs was 1% (95% CI –3% to 5%). Because this confidence interval crosses 1, the difference is not statistically significant. However, the question remains whether the 2 treatments are equivalent given that 80% oxygen is safe and relatively inexpensive and that the real decrease in SSIs may be as great as 3%. Prior to conducting the study, the authors calculated that enrolling 1400 patients would allow an 80% chance of not missing a true difference in SSI rates of 5% (i.e., a decrease from 16% to 11% with the 2 interventions; type-II errors) with a 5% chance of concluding that a difference existed when there really was no difference (type-I error), allowing for a 10% drop-out rate. In reviewing the actual results of the trial, with an event rate of 19%, there was a nearly 80% power to detect a 20% relative risk reduction but only 15% power to detect a 10% relative risk reduction. This finding illustrates that even well constructed studies are unable to confidently exclude a possible treatment effect that is less dramatic.

Therefore, the question of whether there might be a statistically insignificant yet clinically important difference must be answered by each clinician within their own surgical practices. From the results of this study, one would conclude that the treatments are equally effective or equivalent if a difference in SSI rates is considered to be clinically unimportant only if the rate is higher than 4% within 14 days of the index procedure. Furthermore, one cannot conclude that hyperoxia is not beneficial, as this may not be the case in other procedures or settings that were not assessed in this trial. As this therapy remains practical and fairly simple, other populations, such as those excluded from this study with chronic hypoxia, large dedicated colorectal populations or even a primarily elective surgical population, might warrant further investigations.

Competing interests: None declared.

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