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Supplemental oxygen and surgical-site infections: an alternating intervention controlled trial

A. Kurz[1,2], T. Kopyeva[1], I. Suliman[2], A. Podolyak[2,3], J. You[2,4], B. Lewis[1], C. Vlah[1], R. Khatib[1], A. Keebler[1], R. Reigert[3], M. Seuffert[3], L. Muzie[3], S. Drahuschak[3], E. Gorgun[5], L. Stocchi[5], A. Turan[1,2] and D.I. Sessler[2,*]

[1]Department of General Anesthesiology, USA, [2]Department of Outcomes Research, USA, [3]Anesthesiology Institute, USA, [4]Department of Quantitative Health Sciences, USA and [5]Department of Colorectal Surgery, Cleveland Clinic, 9500 Euclid Avenue, P77, Cleveland, OH, 44195, USA

*Corresponding author. E-mail: DS@OR.org.

Abstract

Background: The main defence against bacterial infection is oxidative killing by neutrophils, which requires molecular oxygen in wounded tissues. High inspired-oxygen fractions increase tissue oxygenation. But, whether improving tissue oxygenation actually reduces surgical-site infection (SSI) remains controversial. We therefore tested the primary hypothesis that supplemental oxygen (80% *vs* 30%) reduces the risk of a 30-day composite of deep tissue or organ–space SSI, healing-related wound complications, and mortality.

Methods: In an isolated suite of operating rooms, the inspired-oxygen concentration was alternated between 30% and 80% at 2-week intervals for 39 months. The analysis was restricted to patients who had major intestinal surgery lasting at least 2 h. Qualifying operations (5749) were analysed, including 2843 (49%) colorectal resections, 1866 (32%) lower gastrointestinal therapeutic procedures, 373 (6%) small-bowel resections, and 667 (13%) other colorectal procedures.

Results: The 80% and 30% oxygen groups were well balanced on all of the demographic, baseline, and procedural variables. The oxygen intervention had no effect on the composite primary outcome or any of its components. The overall observed incidence of the composite outcome was 10.8% (314/2896) in the 80% oxygen group and 11.0% (314/2853) in the 30% group. The estimated relative risk was 0.99 (95% CI: 0.85, 1.14) for 80% *vs* 30%, $P=0.85$.

Conclusions: Supplemental oxygen does not prevent major infection and healing-related complications after major intestinal surgery.

Clinical trial registration: NCT01777568.

Key words: anaesthesia; infection; oxygen; surgery

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Editor's key points

- Tissue oxygenation is reliant on adequate perfusion of oxygenated blood; haemoglobin is key.
- Supplemental oxygen had previously been shown to reduce wound infection, but the weight of evidence no longer supports this.
- This study used a novel design, alternating commonly used treatment options in a quality-improvement framework.

The incidence of surgical-site infection (SSI) and complications related to wound healing in colorectal patients is approximately 10–15%.[1] On average, each complication prolongs the duration of hospitalisation by about a week and adds about $5000 to hospital cost of care.[2] Investigators in Denmark, for example, estimate that surgical-wound infections account for 0.5% of the entire country's hospital budget.[3] Patients who develop a wound infection are twice as likely to require intensive-care-unit care and twice as likely to die as those who do not.[2]

The main determinant of whether contamination proceeds to clinical infection is host defence, with the primary defence against surgical pathogens being oxidative killing by neutrophils. Assuming adequate perfusion, the easiest, safest, and most effective way to improve tissue oxygenation is to increase the fraction of inspired oxygen.[4,5] However, there is considerable controversy as to whether supplemental oxygen actually reduces SSI and healing-related complications. Two relatively large randomized trials (n=500 and n=300),[4,6] a smaller trial,[7] and a registry analysis[8] suggest that supplemental oxygen (80% *vs* 30%) halves infection risk. In contrast, the 1400-patient PROXI trial[9] and our recently published 568-patient trial[10] found no benefit of supplemental oxygen. The available literature thus provides no clear guidance on whether supplemental oxygen reduces infection and wound-related complications. Despite considerable divergence in reported results, the World Health Organization recommends that 'adult patients undergoing general anaesthesia with endotracheal intubation for surgical procedures should receive an 80% postoperative period for 2–6 hours to reduce the risk of SSI'.[11] The US Centers for Disease Control and Prevention (CDC) similarly recommends supplemental oxygen to reduce infection risk.[12]

Oxygen management for colorectal surgery remains divergent, reflecting the lack of clear outcome data. In Europe, most patients are given 30% oxygen during general anaesthesia. In the United States, concentrations range from 30% to 100%. At the Cleveland Clinic, the most common concentration is near 50%, but spans the entire range from 30% to 100%. As part of our quality-improvement process, we are developing an enhanced recovery pathway for colorectal surgical patients. One question that arose was whether the pathway should specify inspired-oxygen concentration. The cost of supplemental oxygen is trivial, typically a few cents per patient. And the safety profile of supplemental (80%) oxygen is reasonably well established.[13,14] But, whether providing extra oxygen actually reduces the risk of infectious and other wound complications remains controversial. We, therefore, tested the primary hypothesis that supplemental oxygen (80% *vs* 30% as tolerated) reduces the risk of a 30-day collapsed composite (one or more) of SSI, healing-related wound complications, and mortality.

Methods

The study was restricted to a physically distinct suite of operating rooms, five of which are primarily used by the Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA and are normally staffed by a small group of anaesthesiologists. Furthermore, most operations performed in the suite are substantial and require postoperative hospitalisation. Typically, about 150 major intestinal procedures per month are performed in this suite. Both the anaesthesia and surgical teams agreed to the proposed project. All patients cared for in the designated operating room suite participated.

The designated operating-room suite alternated between using either 30% oxygen as tolerated or 80% oxygen for periods of 2 weeks. For example, the first period used 30% oxygen, the second 80% oxygen, and so on. The oxygen concentration during the initial period was randomly designated by the study statistician. But, thereafter, oxygen delivery was not randomized on a per-patient or even per-period basis. As a safety measure, enough oxygen was always given to maintain oxygen saturation (as determined by pulse oximetry) ≥95%, anticipating that many patients assigned to 30% oxygen would actually require somewhat more. All clinicians retained full authority to use any indicated inspired-oxygen concentration in specific patients per their judgement.

The providers were notified of the designated oxygen concentration for each 2-week period by e-mail notices and signs on each anaesthesia machine. Our decision-support system was also programmed to recognize non-compliant oxygen concentrations and send alerts via the hospital paging system to the in-room provider, the attending anaesthesiologist, and an investigator. The trigger thresholds for 80% weeks were inspired-oxygen concentrations <70% or >90%; the threshold for 30% weeks was an inspired-oxygen concentration >35% and oxyhaemoglobin saturation ≥95%. See Supplemental material for additional details about the benefits and limitations of alternating intervention trials.

There were no other restrictions on anaesthetic management, and practitioners were free to use i.v. anaesthetics and neuraxial analgesia per their preference. Positive end-expiratory pressure (PEEP) was not controlled, but was typically set to 5 cm H_2O. All surgical patients at the Cleveland Clinic are warmed with forced air intraoperatively; prewarming was not used. Mechanical bowel preparation was used selectively and was usually accompanied by oral antibiotics taken the day before surgery. Oral antibiotic prophylaxis, when used, typically consisted of neomycin 1000 mg and metronidazole 500 mg at 9:00 PM and repeated at 11:00 PM the night before the surgery. Prophylactic i.v. antibiotics were given intravenously within an hour before incision, according to the Surgical Care Improvement Project guidelines.[15] There were no major changes in surgical or anaesthetic management during the study period, for example, activation of a new enhanced recovery pathway.

Measurements

All values used in the analysis were obtained from various registries, including patient and morphometric characteristics. The type of surgery was characterized from the Current Procedural Terminology codes using the Agency for Healthcare Research and Quality Clinical Classifications Software (Rockville, MD, USA). All routine anaesthetic variables,