Increasing Inspired Oxygen to Decrease Surgical Site Infection

Time to Shift the Quality Improvement Research Paradigm

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PATIENTS WHO DEVELOP A SURGICAL SITE INFECTION (SSI) have a 2-fold increase in the length of hospital stay and the risk of death[1] and cost the US health care system approximately $1.8 billion per year.[2] SSI is the most common preventable adverse outcome after a major operation and is the focus of several major national and international quality improvement initiatives. There is no absolute method to prevent SSI, but more than 30 years of research have shown that proper antibiotic selection and timing, clipping rather than shaving of hair, maintenance of normothermia and normoglycemia, and appropriate surgical technique are critical to reduce the risk.[3] For years, surgeons have debated the benefits of higher levels of inspired oxygen in reducing SSI. In this issue of *JAMA*, Belda and colleagues[4] report the results of their clinical trial using different inspired oxygen concentrations intraoperatively and for 6 hours after surgery in patients undergoing planned open (nonlaparoscopic) colorectal operations.

The study by Belda et al was performed in 14 Spanish hospitals and the primary outcome was superficial or deep SSI. The overall infection rate was 20% and was significantly reduced in the group of patients receiving 80% fraction of inspired oxygen (F_{IO_2}) compared with the group receiving 30% F_{IO_2} (infection rates of 15% vs 24%, respectively). The absolute risk reduction was 9%, with a relative risk reduction of 39%. If these results are generalizable, the findings have important implications. For instance, with an estimated 600 000 SSIs per year for major surgery in the United States alone, at an estimated cost of $1.8 billion,[2] a 39% reduction would represent a dramatic improvement in terms of reducing both morbidity and cost.

The concept of influencing the risk of SSI by increasing oxygen concentration is attractive, based on the principle that infection risk is dependent on the number of bacteria that reach the surgical wound during an operation and on the host's ability to kill those bacteria during the early wound healing events that follow in the first hours after wounding.[5] One of the primary mechanisms of early bacterial eradication involves oxidative processes in polymorphonuclear leukocytes that depend on oxygen tension.[6] The quantity of oxygen used is small and the processes depend more on oxygen tension at the wound than on oxygen delivery. In vitro studies,[7,8] animal studies,[7,9-13] and observational studies in humans[14] support the value of increased oxygen tension in tissues. Local or systemic warming of patients, which increases oxygen tension,[15-19] also decreases infection risk.[19,20] Thus, there is a strong theoretical rationale for the results of this trial.

See also p 2035.

The situation becomes more complicated when data from 2 other clinical trials are examined. Greif et al[21] studied 500 patients undergoing open colorectal operations. Patients received either 30% or 80% F_{IO_2} intraoperatively and for 2 hours after surgery, and preoperative, intraoperative, and postoperative preparation, temperature management, and anesthetic and fluid management were standardized. The overall infection rate was 8%, with infection rates of 11.2% in the group that received 30% F_{IO_2} compared with 5.2% in the group that received 80% F_{IO_2} ($P<.01$). The absolute risk reduction was 6%, with a relative risk reduction of 54%.

Pryor et al[22] enrolled 160 patients from 1 US hospital who underwent a variety of open abdominal procedures, including colectomy, gastrectomy, hepatobiliary surgery, and gynecological and urological procedures, and received either 35% or 80% F_{IO_2} concentrations in the operating room and for 2 hours after surgery. The authors intentionally included a variety of procedures and did not standardize perioperative treatment (to reflect practice variation in the real world). The overall infection rate was 18%, with an infection rate of 25% in the high oxygen concentration group and 11% in the low oxygen group. The high oxygen group had an absolute *increase* of 14% with a relative increase of 121%.

Several factors may help to explain the dramatically different results of this study. For instance, the patient groups in the study by Pryor et al were not as well matched as those in the studies by Greif et al or Belda et al, and blinding and other aspects of study conduct were not as rigorous. In the study by Pryor et al, the end point was determined by retrospective chart review by questionably blinded investigators, there was an imbalance in the intervention and control groups with regard to obesity and other important covariates, and the overall sample size was relatively small.

Faced with these conflicting data, what should a surgeon and anesthesiologist do? One conclusion is that the

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trials by Belda et al and Greif et al that studied colorectal procedures exclusively both showed clear advantages for high inspired oxygen concentrations and that, therefore, 80% oxygen concentrations should be recommended for patients having colorectal operations. However, it defies logic that colorectal operations should have a biologically opposite response to oxygen concentrations compared with other abdominal procedures.

The limitations and smaller sample size of the study by Pryor et al are insufficient to counterbalance the 2 more rigorously performed and larger randomized controlled trials. If the results of these 3 studies are pooled, the combined experience of the 3 studies reveals that of 473 patients receiving either 30% or 35% oxygen, 72 (15.2%) had an SSI, while of the 478 patients receiving 80% oxygen, 55 (11.5%) had an SSI. This is an absolute risk reduction of 3.7% and a relative risk reduction of 24% (P for the difference=.10). Pooling the data from Belda et al and Greif et al may be more appropriate and demonstrate an absolute risk reduction of 7%, with a relative risk reduction of 45% (P=.002).

Nonetheless, the pooled data from all 3 studies do not show any risk associated with increased oxygen concentrations but suggest possible benefit. Moreover, that benefit has a substantial biological rationale and abundant supporting data from in vitro, animal, and observational human studies. One approach to this conundrum may be to change the paradigm by which interventions aimed at reducing important adverse outcomes are evaluated. For interventions that cost little, have low risk profiles, and appear to be effective in rigorous trials, it seems reasonable to encourage their use until overwhelming evidence suggests that they do not work or are not worth the cost. Defending the status quo (low oxygen tension) by demanding the perfect study to reconcile the "2 out of 3 studies support" problem with 80% FIO_2 may be missing a quality improvement opportunity precisely at the time when the surgical community is embracing evidence-based approaches to improve quality. Additional, larger trials addressing these issues need to be performed. Addressing this question merits National Institutes of Health support. However, surgeons should not wait for this issue to be resolved before moving forward with this simple, inexpensive, and low-risk intervention while at the same time monitoring both its effectiveness in the community at large and the chance that its use will have unintended consequences.

In the meantime, a large number of other factors and interventions are known to influence risk for SSI in operative patients. For many of these interventions, there is essentially no controversy, and yet they are not being consistently delivered to patients. Recent surveys of actual practice in the United States show that proper choice of prophylactic antibiotic, timing of antibiotic delivery, avoidance of shaving the surgical site, keeping the patient warm in the operating department, and maintaining normoglycemia are not achieved in 10% to 55% of patients.[2,23] Recent quality improvement SSI surveillance data from 1 hospital has demonstrated that when an SSI does occur, in more than 70% of the cases, known preventive measures, such as antibiotic delivery and maintenance of normothermia, were not achieved (E.P.D., unpublished data, 2005). A focused effort to change these conditions can result in a dramatic reduction in SSI.[23]

Surgeons and members of surgical teams should all be working in these areas until more definitive information about oxygen concentrations in the operating department becomes available. Surgeons should encourage the broader use of higher oxygen tensions for their patients undergoing major abdominal procedures and be more involved in quality improvement initiatives aimed at reducing SSI.

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