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Long-term Consequences of Anesthetic Management

Editor's Note: This is the first in a series of four Editorial Views on long-term outcomes after anesthesia and surgery. This series adds to other recent Editorial Views in ANESTHESIOLOGY and includes a discussion of broadening our research outside of the operating room to prevention of wound infections, cancer spread, cardiovascular morbidity and mortality, chronic postsurgical pain, and rare complications. ANESTHESIOLOGY will sponsor special sessions in 2010 on the topic of long-term outcomes at annual meetings of the Japanese Society of Anesthesiologists, the European Society of Anesthesiology, and the American Society of Anesthesiologists.

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TWENTY-FIVE years ago, when I was an anesthesia resident, preventable anesthetic mortality occurred in perhaps 1 of 10,000 cases[1]—making anesthesia the most dangerous part of most operations. I refer neither to the patients who died of overwhelming underlying disease nor to the patients who died of acute surgical misadventures; I mean relatively healthy patients having routine operations who died from anesthetic causes and mistakes.

High anesthetic mortality in the early 1980s was perhaps unsurprising considering the state of anesthesia equipment, drugs, and training. Anesthesia machines often lacked a nitrous oxide-oxygen interlock; on such machines, there was little to prevent an anesthesiologist at the end of the case from turning off the oxygen instead of the nitrous oxide—thus delivering a hypoxic gas mixture. And having done so, the error was often undetected until too late because oxygen analyzers were not uniformly used.

Volatile anesthetics in that era were still often delivered *via* copper kettles, which meant that reductions in fresh gas flow proportionately increased delivered anesthetic concentration, sometimes to dangerous levels. Such episodes would rarely be detected because expired gas monitoring was restricted to a limited number of academic centers that had invested in expensive and touchy multiplexed mass spectrometry systems. Pulse oximetry was yet to be available for some years hence. Available drugs were longer-acting and harder to use than our current ones; the less-soluble volatile anesthetic in those days was isoflurane, halothane remained in common use, and the shorter-acting muscle relaxant was curare. Furthermore, anesthesia residency was only 2 yr and considerably less rigorous than it is now.

My, how it has changed! Preventable anesthetic mortality is now probably less than 1 case in 100,000,[1,2] a more than 10-fold improvement that earned our specialty a "most improved" designation from the Institute of Medicine.[3] (Granted, evaluating anesthetic mortality remains inexact and controversial,[4,5] but the consensus is that improvement has been substantial in recent decades, especially considering how much sicker patients are now.) An unfortunate consequence of our improvement is that some consider anesthetic safety a more-or-less solved problem. At the very least, the number of intraoperative deaths is now so small that policymakers might reasonably conclude that resources would be better invested elsewhere. This thought process may contribute to the dismally small amount of funding that the National Institutes of Health provides for anesthesiology research.

Long-term Outcomes

In distinct contrast to preventable anesthetic mortality, which thankfully is now rare, all-cause postoperative mortality is surprisingly high. About 5% of all surgical patients die in the year after surgery; among those aged more than 65 yr, mortality is about 10%.[6] To put this another way, mortality in the year after surgery is about 10,000 times more common than preventable anesthetic mortality.

It is thus reasonable to ask to what extent anesthetic management might influence long-term outcomes. The distinction I make here is between the classic definition of anesthetic complications, which is restricted to the immediate perioperative period extending perhaps to a few days after surgery, and the potential effects of anesthetic management on events weeks, months, or even years after surgery.

Given that modern anesthetic drugs are uniformly short-acting, it is by no means obvious that consequences of anesthetic management could last more than hours or days after surgery. Certainly, long-term consequences of anesthesia were not seriously considered until relatively recently. That said, however, there is increasing evidence that some intraoperative anesthetic management decisions do have long-term consequences and that others might as well.

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Surgical Site Infection

Arguably, the first convincing evidence for long-term outcomes related to anesthetic management dates to 1996, which saw publication of two key articles in the *New England Journal of Medicine*. One, from Mangano *et al.*, linked perioperative β-blocker administration to myocardial infarction and mortality[7] (more about this topic below). The other, from Kurz *et al.*, showed that mild hypothermia triples the risk of surgical wound infection[8] even though surgical site infections become clinically apparent 1–4 weeks after surgery. The link between hypothermia and infection was subsequently confirmed by an additional randomized trial.[9] The risk of surgical wound infection also appears to be moderated by supplemental oxygen, even when supplemental oxygen is only provided during surgery and 2 or 6 hr thereafter.[10,11]

There is thus considerable evidence that wound infections, despite becoming clinically apparent weeks after surgery, are established during and immediately after surgery. All surgical wounds become contaminated; surgical sterility is only relative! Whether contamination progresses to a clinical infection is determined by the adequacy of host defenses during a decisive period lasting some hours after contamination. In the case of bacteria causing surgical wound infections, the most important host defense is oxidative killing by neutrophils.[12] This process requires molecular oxygen[13] and is a function of tissue (as opposed to arterial) oxygen partial pressure over the entire physiologic range. Interventions that increase tissue oxygen during the decisive period, such as maintaining normothermia[14] and providing supplemental oxygen,[10] reduce progression of contamination to clinical infection.

It is likely that infection risk is similarly diminished by other factors that support tissue oxygenation,[15] including adequate sympathetic block[16] and good control of surgical pain.[17] The potential benefit of these and other interventions have yet to be determined in large- scale outcome studies, but they remain under active investigation.

Regional Analgesia and Cancer Recurrence

An additional long-term outcome to consider is cancer. Although not widely appreciated, tumor surgery is usually associated with release of tumor cells into the lymphatic and blood streams; furthermore, a large fraction of patients already harbor micrometastases and scattered tumor cells at the time of surgery.[18] Whether this *minimal residual disease* results in clinical metastases depends largely on the balance between antimetastatic immune activity and the tumor's ability to seed, proliferate, and attract new blood vessels.[19]

At least three perioperative factors shift the balance toward progression of minimal residual disease. The first is surgery *per se*, which releases tumor cells into circulation,[18] depresses cell-mediated immunity including cytotoxic T-cell and natural killer cell functions,[20] reduces circulating concentrations of tumor-related antiangiogenic factors, increases concentrations of proangiogenic factors such as vascular endothelial growth factor,[21] and releases growth factors that promote local and distant growth of malignant tissue.[19] The second factor is that volatile anesthesia *per se* impairs neutrophil, macrophage, dendritic-cell, T-cell, and natural killer-cell immune functions.[22] The third factor is opioids that inhibit both cellular and humoral immune function.[22] Furthermore, morphine is proangiogenic and promotes tumor growth.[23] Consequently, nonopioid analgesia helps preserve natural killer cell function in animals and humans and reduces metastatic spread of cancer in rodents.[24]

Regional anesthesia and analgesia attenuate or prevent each of these adverse effects. For example, regional anesthesia largely prevents the neuroendocrine stress response to surgery by blocking afferent neural transmission from reaching the central nervous system and by blocking descending efferent activation of the sympathetic nervous system.[25] Consequently, natural killer-cell function is better preserved with regional anesthesia and metastatic load to the lungs is reduced in a rat model of breast cancer metastasis.[20]

When regional and general anesthetics are combined, the amount of general anesthetic required is much reduced, as is presumably immune suppression. Furthermore, regional analgesia provides superb pain relief, essentially obviating the need for postoperative opioids, and the consequent adverse effects on immune function and of tumor growth.[22,25] Regional analgesia also reduces release of endogenous opioids.[26]

Available data thus suggest that regional anesthesia and analgesia help preserve effective defenses against tumor progression by attenuating the surgical stress response, by reducing general anesthesia requirements, and by sparing postoperative opioids.[27] Animal studies are consistent with this theory, showing that regional anesthesia and optimum postoperative analgesia independently reduce the metastatic burden in animals inoculated with breast adenocarcinoma cells.[28] Available human data, although extremely limited, are also consistent with this theory. For example, paravertebral anesthesia and analgesia for breast cancer surgery is associated with an approximately four-fold reduced risk of recurrence or metastasis.[29] Similarly, epidural analgesia for radical prostate surgery is associated with a 60% reduction in recurrence risk.[30] Major prospective trials of paravertebral analgesia for breast cancer surgery (NCT00418457)[31] and epidural analgesia for colon cancer are in progress (NCT00684229).

Recent and Future Editorials Exploring Long-term Outcomes

Additional proven or potential long-term outcomes of perioperative management have already been addressed in recent ANESTHESIOLOGY editorials. For example, an editorial in the December issue by Spahn *et al.* highlights the dangers of red cell transfusions, especially noninfectious complications, which are the major risk.[32] Editorials in the February (Fahy *et al.*[33] and Nunnally and O'Conner[34]) and March (Lanier and Pasternak[35]) issues discuss the risks and benefits of tight glycemic control. Also in March, Kehlet and Bundgaard-Nielsen discuss long-term consequences of perioperative fluid management.[36] An editorial by Maze focused on postoperative cognitive dysfunction.[37] And finally, April editorials by Patel and Sun[38] and by Perouansky and Hemmings[39] dealt with volatile anesthetic toxicity in newborns.

This is the first of four editorials to address additional potential long-term consequences of anesthetic management. The next will be by Philip Devereaux, M.D., Ph.D., from the Department of Clinical Epidemiology and Biostatistics and Medicine, McMaster University in West Hamilton, Ontario, Canada, who will present the evidence linking β-blocker administration and sympatholysis with perioperative myocardial infarction, stroke, and mortality. Devereaux was the principal investigator on the recent POISE trial, which is by far the largest randomized trial of perioperative β-blocker use.[40] Marc De Kock, M.D., Ph.D., Department of Anesthesiology, Universite Catholique de Louvain, St. Luc Hospital, Brussels, Belgium, who has published extensively on the topic, will then discuss persistent incision pain. Finally, Alexander Hannenberg, M.D., of the Department of Anesthesiology, Newton-Wellesley Hospital, Tufts University School of Medicine, Newton, Massachusetts, and Mark Warner, M.D., of the Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota, will discuss how the new Anesthesia Quality Institute and Maintenance of Certification in Anesthesiology may improve long-term anesthetic outcomes. As leaders of these initiatives, they are well positioned to put them into perspective.

Finally, I am delighted to announce that long-terms outcomes will be the topic of the 2010 ANESTHESIOLOGY Journal Symposium. We look forward to an in-depth exploration of this exciting new dimension of anesthesia.

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ANESTHESIOLOGY REFLECTIONS

Hingson's Peace Gun

Familiar with jet-injection injuries from his military background, Anesthesiologist Robert A. Hingson, M.D. (1913–1996) published about needle-free injection as early as 1947. By the following year, Hingson had penned papers about his "Hypospray" device, nearly 20 years before Hyposprays were featured on television's *Star Trek* and then in more than a dozen unrelated science fiction movies. Surprisingly, this handheld version of a Hingson "Peace Gun" pictured above—with its luger-like metal silhouette and sharp bottle piercer— went unchallenged through airport security x-ray machines as it was curatorially hand-carried to the gallery of the Wood Library-Museum. Facilitated by patent innovations in the 1960s by Aaron Ismach and others, Hingson and his Cleveland and Pittsburgh colleagues popularized jet injection technologies which have immunized more than a billion people and eradicated smallpox worldwide. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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