

Neuraxial Anesthesia and Surgical Site Infection

Surgical site infections remain among the most common serious perioperative complications. The overall incidence is 1–3%, but the risk is 10% or more for colon resections.¹ Deep-tissue and organ-space infections, and those involving implanted hardware, are especially serious. For example, the overall infection rate in a representative sample of patients undergoing hip and knee replacements in Taiwan is reported to be 1.8% in this issue of ANESTHESIOLOGY.²

Neither operating rooms nor patients are perfectly sterile. Thus, all surgical wounds become contaminated. Although the type and degree of contamination clearly matter, progression from contamination to clinical infection is largely determined by the adequacy of host defense. Oxidative killing by neutrophils is by far the most important defense.³ Oxidative killing is a function of local tissue oxygenation, which in turn is determined by arterial oxygen partial pressure, perfusion, and local rate of oxygen extraction.⁴ Tissue oxygenation is generally thought to be the best single predictor of infection risk.⁵

One strategy for preventing surgical site infections is to reduce contamination by timely⁶ administration of appropriate short-course⁷ or single-dose⁸ antibiotics, which should be repeated during prolonged procedures.⁹ Other well-established approaches include clipping rather than shaving the skin,¹⁰ topical decontamination in nasal carriers of *Staphylococcus*,¹¹ and use of chlorhexidine–alcohol surgical scrub solutions.¹²

The other general approach for reducing infection risk is to use anesthetic strategies that maintain or even enhance host defense. For example, allowing surgical patients to become hypothermic both reduces tissue oxygenation¹³ and either impairs^{14,15} or enhances¹⁶ various immune functions. As might thus be expected, maintaining normothermia reduces infection risk by a factor of three.^{17,18} Erythrocyte transfusions—and especially transfusion of cells after prolonged storage—provoke a nonspecific inflammatory response,¹⁹ which may divert the immune system from a more appropriate focus on the very real threat posed by bacterial contamination.²⁰ Minimizing erythrocyte transfusions,^{21,22} and transfusing cells stored less than 2 weeks,²³ therefore reduces infection risk.

Supplemental oxygen has the potential to enhance host defense against bacteria by augmenting tissue oxygenation to supernormal partial pressures. Increasing the fraction of in-

spired oxygen (*i.e.*, 80% *vs.* 30%) doubles tissue oxygenation from ≈ 60 to ≈ 110 mmHg²⁴ without causing atelectasis.²⁵ Studies in 500 and 300 patients, respectively, reported that supplemental oxygen halves infection risk^{24,26}; however, a subsequent study in 1,400 patients found no benefit.²⁷ The effect of supplemental oxygen on surgical site infection, thus, remains unclear.

Chang *et al.* proposed another preventive approach: use of neuraxial rather than general anesthesia. At least three potential mechanisms make the strategy plausible. The first is that neuraxial anesthesia moderates the inflammatory response to surgery; as mentioned earlier, reducing nonspecific generalized responses may allow the immune system to focus better on the critical task of fighting bacteria.²⁸ The clinical importance of this mechanism remains essentially unknown.

A second mechanism by which neuraxial anesthesia might reduce infection is *via* vasodilation and consequent improvement in tissue oxygenation. Several studies document small (*i.e.*, 10 mmHg) increases in tissue oxygen when epidural anesthesia was compared with the combination of epidural and general anesthesia,^{29–31} although another that compared epidural anesthesia with general anesthesia reported no effect on tissue oxygenation.³² Thus, available evidence suggests that neuraxial anesthesia at best only slightly increases tissue oxygenation. However, it remains possible that differences would be greater if tissue oxygenation during general anesthesia was compared with neuraxial anesthesia alone—rather than with combined neuraxial–general anesthesia as in the previous studies.

The third mechanism by which neuraxial anesthesia, especially epidural anesthesia, could reduce infection risk is by providing excellent postoperative analgesia. Severe pain provokes an autonomic response, which, in turn, causes vasoconstriction and reduced peripheral perfusion. Unsurprisingly, severe surgical pain, therefore, reduces tissue oxygenation by ≈ 15 mmHg.³³

Although none of these potential mechanisms is entirely convincing, some combination of the three may substantially reduce infection risk. Certainly, the factor-of-two reduction Chang *et al.* report is of considerable clinical importance. To put it in perspective, this reduction is similar to that produced by timely antibiotic administration.

◆ This Editorial View accompanies the following article: Chang C-C, Lin H-C, Lin H-W, Lin H-C: Anesthetic management and surgical site infections in total hip or knee replacement: A population-based study. ANESTHESIOLOGY 2010; 113:279–84.

Accepted for publication April 6, 2010. The author had no personal financial interest in any commercial activity associated with the topic of this article.

One major approach to clinical research is the familiar randomized trial. The major advantage of this approach is that randomization and blinding provide considerable protection against bias and confounding. However, controlled trials usually restrict enrollment to patients most likely to benefit from the test intervention and least likely to suffer harm. Furthermore, treatment pathways are explicit and enforced. A consequence is that results from controlled efficacy trials often generalize poorly to larger populations and routine practice. Randomized trials are also expensive and, thus, sometimes only marginally powered.

The other major approach to clinical research, the one used by Chang *et al.*, is to use epidemiologic and statistical techniques to evaluate the effects of treatments in “real-world” situations. A major advantage of effectiveness trials is generalizability, and this is especially a strength for Chang *et al.* because their analysis is based on a random sample of nearly all surgical cases in Taiwan. Thus, the results at the very least apply to Taiwan but presumably can be extrapolated to other developed healthcare systems.

Selection bias occurs when treatments are allocated non-randomly. Neuraxial anesthesia surely was not randomly allocated in the patients considered by Chang *et al.* The question, though, is whether patients given neuraxial anesthesia had a lower baseline infection risk than those given general anesthesia. Among the patient and surgical characteristics available to the investigators, there were no clinically important differences. Furthermore, their statistical model is adjusted for known differences. The difficulty is that unknown differences may have contributed to an apparent protective effect of neuraxial anesthesia. For example, smoking, steroid use, alcohol abuse, and low plasma albumin concentration are all highly correlated with infection risk,³⁴ but apparently they were unavailable to the investigators. Thus, it remains possible—although perhaps unlikely—that patients with these characteristics were nonrandomly allocated to neuraxial anesthesia.

Measurement bias occurs when outcome assessments are both erroneous and nonrandomly distributed between treatment groups. Both are required: measurement error *per se* does not constitute bias so long as the inaccuracy is comparable in each group. Thus, undercounting infections, for example, would uniformly reduce the apparent incidence but not the relative risk reduction associated with neuraxial anesthesia. It seems likely that the administrative records available to Chang *et al.* undercounted less severe infections; but there is little reason to suppose that infections—which typically occur a week or more after surgery—would be systematically underreported in patients who had neuraxial anesthesia.

Confounding occurs when an intervention such as neuraxial anesthesia and an outcome such as infection are linked by a third (noncausal) factor. The danger is that the linking factor may not have been evaluated or may not even be known. Consider temperature, for example: hypothermia increases infection risk,^{17,18} but intraoperative temperatures were not available to the investigators and, therefore, not included in their multivariable analysis. Now let us suppose

that warming was not routine during the years of the study but that many neuraxial patients were warmed because they were conscious and complained about being in cold operating rooms. Patients given neuraxial anesthesia would consequently more often be normothermic and, therefore, less likely to develop surgical site infections but for reasons completely independent of neuraxial anesthesia.

Similarly, consider postoperative nausea and vomiting, which are rare after neuraxial anesthesia but occur in approximately 30% of patients recovering from general anesthesia.³⁵ Patients given general anesthesia are, thus, much more likely to have also been given prophylactic drugs to reduce postoperative nausea and vomiting. Dexamethasone is among the effective prophylactic measures³⁶ but also suppresses the immune system and may, therefore, increase infection risk. To the extent that it was used more often in patients given general anesthesia and to the extent that it increases infection risk (which is by no means proven), more infections in the general anesthesia patients may be explained by dexamethasone administration rather than general anesthesia *per se*. Perhaps, neither example is likely; but other known or unknown factors might also have confounded the results, including vascular volume management or glucose control.

Well-established methods of reducing surgical site infection risk include appropriate antibiotic use, clipping rather than shaving hair, using chlorhexidine–alcohol surgical scrub solutions, avoiding transfusions (especially with older blood), and maintaining normothermia. Nonetheless, surgical site infections remain a common and serious long-term complication of anesthesia and surgery. Chang *et al.* now provide compelling epidemiologic evidence that the use of neuraxial anesthesia also reduces risk.

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