Anesthesiology 2010; 113:265–7

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 timely[6] administration of appropriate short-course[7] or single-dose[8] 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 oxygenation[13] and either impairs[14,15] or enhances[16] 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 inspired oxygen (*i.e.*, 80% *vs.* 30%) doubles tissue oxygenation from ≈60 to ≈110 mmHg[24] 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 nonrandomly. 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 measures[36] 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.

Daniel I. Sessler, M.D., Department of Outcomes Research, The Cleveland Clinic, Cleveland, Ohio. ds@or.org

References

1. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ: The impact of surgical-site infections in the 1990s: Attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol 1999; 20: 725–30
2. Chang C-C, Lin H-C, Lin H-W, Lin H-C: Anesthestic management and surgical site infections in total hip or knee replacement: A population-based study. ANESTHESIOLOGY 2010; 113:279–84
3. Benhaim P, Hunt TK: Natural resistance to infection: Leukocyte functions. J Burn Care Rehabil 1992; 13:287–92
4. Hopf HW, Jensen JA, Hunt TK: Calculation of subcutaneous tissue blood flow. Surg Forum 1988; 39:33–6
5. Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH III, Jensen JA, Jonsson K, Paty PB, Rabkin JM, Upton RA, von Smitten K, Whitney JD: Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg 1997; 132:997–1004; discussion 1005
6. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP: The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992; 326:281–6

7. Harbarth S, Samore MH, Lichtenberg D, Carmeli Y: Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. Circulation 2000; 101:2916–21
8. McDonald M, Grabsch E, Marshall C, Forbes A: Single-*versus* multiple-dose antimicrobial prophylaxis for major surgery: A systematic review. Aust N Z J Surg 1998; 68: 388–96
9. Zanetti G, Giardina R, Platt R: Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery. Emerg Infect Dis 2001; 7:828–31
10. Alexander JW, Fischer JE, Boyajian M, Palmquist J, Morris MJ: The influence of hair-removal methods on wound infections. Arch Surg 1983; 118:347–52
11. Bode LG, Kluytmans JA, Wertheim HF, Bogaers D, Vandenbroucke-Grauls CM, Roosendaal R, Troelstra A, Box AT, Voss A, van der Tweel I, van Belkum A, Verbrugh HA, Vos MC: Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med 2010; 362:9–17
12. Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH: Chlorhexidine-alcohol *versus* povidone-iodine for surgical-site antisepsis. N Engl J Med 2010; 362:18–26
13. Sheffield CW, Sessler DI, Hopf HW, Schroeder M, Moayeri A, Hunt TK, West JM: Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. Wound Rep Reg 1997; 4:339–45
14. Wenisch C, Narzt E, Sessler DI, Parschalk B, Lenhardt R, Kurz A, Graninger W: Mild intraoperative hypothermia reduces production of reactive oxygen intermediates by polymorphonuclear leukocytes. Anesth Analg 1996; 82: 810–6
15. Akriotis V, Biggar WD: The effects of hypothermia on neutrophil function *in vitro*. J Leukoc Biol 1985; 37:51–61
16. Frohlich D, Wittmann S, Rothe G, Sessler DI, Vogel P, Taeger K: Mild hyperthermia down-regulates receptor-dependent neutrophil function. Anesth Analg 2004; 99:284–92
17. Kurz A, Sessler DI, Lenhardt RA: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infections and Temperature Group. N Engl J Med 1996; 334:1209–15
18. Melling AC, Ali B, Scott EM, Leaper DJ: Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomised controlled trial. Lancet 2001; 358:876–80
19. Fransen E, Maessen J, Dentener M, Senden N, Buurman W: Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. Chest 1999; 116:1233–9
20. Ho J, Sibbald WJ, Chin-Yee IH: Effects of storage on efficacy of red cell transfusion: When is it not safe? Crit Care Med 2003; 31:S687–97
21. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH: Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006; 34:1608–16
22. Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P: Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. ANESTHESIOLOGY 2008; 108:31–9
23. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH: Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008; 358:1229–39
24. Greif R, Akça O, Horn E-P, Kurz A, Sessler DI: Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. N Engl J Med 2000; 342:161–7
25. Akça O, Podolsky A, Eisenhuber E, Panzer O, Hetz H, Lampl K, Lackner FX, Wittmann K, Grabenwoeger F, Kurz A, Schultz A-M, Negish C, Sessler DI: Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and for two hours after colon resection. ANESTHESIOLOGY 1999; 91:991–8
26. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, Rodriguez R, Company R, Sessler DI, Aguilar G, Botello SG, Orti R: Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. JAMA 2005; 294:2035–42
27. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Simonsen I, Pulawska T, Walker LR, Skovgaard N, Helto K, Gocht-Jensen P, Carlsson PS, Rask H, Karim S, Carlsen CG, Jensen FS, Rasmussen LS: Perioperative oxygen fraction—effect on surgical site infection and pulmonary complications after abdominal surgery: A randomized clinical trial. Rationale and design of the PROXI-Trial. Trials 2008; 9:58
28. Ciepichal J, Kubler A: Effect of general and regional anesthesia on some neutrophil functions. Arch Immunol Ther Exp (Warsz) 1998; 46:183–92
29. Kabon B, Fleischmann E, Treschan T, Taguchi A, Kapral S, Kurz A: Thoracic epidural anesthesia increases tissue oxygenation during major abdominal surgery. Anesth Analg 2003; 97:1812–7
30. Treschan TA, Taguchi A, Ali SZ, Sharma N, Kabon B, Sessler DI, Kurz A: The effects of epidural and general anesthesia on tissue oxygenation. Anesth Analg 2003; 96: 1553–7
31. Buggy DJ, Doherty WL, Hart EM, Pallett EJ: Postoperative wound oxygen tension with epidural or intravenous analgesia: A prospective, randomized, single-blind clinical trial. ANESTHESIOLOGY 2002; 97:952–8
32. Rosenberg J, Pedersen U, Erichsen CJ, Vibits H, Moesgaard F, Kehlet H: Effect of epidural blockade and oxygen therapy on changes in subcutaneous oxygen tension after abdominal surgery. J Surg Res 1994; 56:72–6
33. Akça O, Melischek M, Scheck T, Hellwagner K, Arkiliç C, Kurz A, Kapral S, Heinz T, Lackner FX, Sessler DI: Postoperative pain and subcutaneous oxygen tension. Lancet 1999; 354:41–2
34. Neumayer L, Hosokawa P, Itani K, El-Tamer M, Henderson WG, Khuri SF: Multivariable predictors of postoperative surgical site infection after general and vascular surgery: Results from the patient safety in surgery study. J Am Coll Surg 2007; 204:1178–87
35. Apfel CC, Kranke P, Eberhart LH: Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting. Anaesthesia 2004; 59:1078–82
36. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI, Roewer N: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004; 350:2441–51