The long-term consequences of anaesthetic management

Sessler DI, MD
Michael Cudahy Professor and Chair, Department of Outcomes Research
Correspondence to: Daniel Sessler, e-mail: ds@or.org
Keywords: long-term consequences, anaesthetic management

 South Afr J Anaesth Analg 2014;20(1):52-54

Introduction

In distinct contrast to preventable anaesthetic mortality, which thankfully is now rare, all-cause postoperative mortality is surprisingly high. Approximately 5% of surgical patients die in the year following surgery. Mortality is roughly 10% in those who are older than 65 years of age.[1] In other words, mortality in the year after surgery is approximately 10 000 times more common than preventable anaesthetic mortality.

Thus, it is reasonable to ask to what extent anaesthetic management might influence long-term outcomes. The distinction being made here is between the classical definition of anaesthetic complications, which is restricted to the immediate perioperative period, perhaps extending to a few days after surgery, and the potential effects of anaesthetic management on events weeks, months or even years after surgery.

Given that modern anaesthetic drugs are uniformly short acting, it is by no means obvious that the consequences of anaesthetic management could last more than hours or days after surgery. The long-term consequences of anaesthesia were not seriously considered until relatively recently. There is increasing evidence that some intraoperative anaesthetic management decisions have long-term consequences, and that others might as well.

Surgical site infection

Arguably, the first convincing evidence of long-term outcomes that relate to anaesthetic management dates to 1996 when two key articles were published in the *New England Journal of Medicine*. Mangano et al linked perioperative beta-blocker administration to myocardial infarction and mortality.[2] Kurz et al showed that mild hypothermia tripled the risk of surgical wound infection,[3] 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 randomised trial.[4] The risk of surgical wound infection also appeared to be moderated by supplemental oxygen, even when supplemental oxygen was only provided during surgery, and at two[5] or six[6] hours thereafter.

Thus, there is considerable evidence that wound infections, despite becoming clinically apparent weeks after surgery, are established during and immediately after surgery. Surgical wounds become contaminated and surgical sterility is only relative! Whether or not contamination progresses to clinical infection is determined by the adequacy of host defenses during a decisive period that lasts several hours after contamination. The most important host defense is oxidative killing by neutrophils in the case of bacteria which causes surgical wound infections.[7] This process requires molecular oxygen[8] and is a function of tissue, as opposed to arterial oxygen partial pressure over the entire physiological range. Interventions which increase tissue oxygen during the decisive period, such as maintaining normothermia[9] and providing supplemental oxygen,[5] reduce the progression of contamination to clinical infection.

It is likely that infection risk is similarly diminished by other factors that support tissue oxygenation,[10] including adequate sympathetic block[11] and good control of surgical pain.[12] The potential benefit of these and other interventions has yet to be determined in large-scale outcome studies, but remain under active investigation.

Regional analgesia and cancer recurrence

Cancer is an additional long-term outcome that needs to be considered. Although not widely appreciated, tumour surgery is usually associated with the release of tumour cells into the lymphatic and blood streams. Furthermore, a large fraction of patients already harbour micrometastases and scattered tumour cells at the time of surgery.[13] Whether this minimal residual disease results in clinical metastases depends largely on the balance between antimetastatic immune activity and the tumour's ability to seed, proliferate and attract new blood vessels.[14]

At least three perioperative factors shift the balance towards the progression of minimal residual disease:

- The first is surgery, which releases tumour cells into circulation;[13] depresses cell-mediated immunity (including cytotoxic T-cell and natural killer cell functions);[15] reduces circulating concentrations of tumour-related antiangiogenic factors; increases concentrations of proangiogenic factors, such as vascular endothelial growth factor;[16] and releases growth factors which promote the local and distant growth of malignant tissue.[14]
- The second factor is that anaesthesia impairs neutrophil, macrophage, dendritic cell, T-cell, and natural killer cell immune functions.[17]
- The third is opioids which inhibit both cellular and humoral immune function.[17] Furthermore, morphine is proangiogenic and promotes breast tumour growth.[18] Consequently, non-opioid analgesia helps to preserve natural killer cell function in animals and humans, and reduces the metastatic spread of cancer in rodents.[19]

Regional anaesthesia and analgesia (postoperative pain relief) attenuate or prevent each of these adverse effects. For example, regional anaesthesia 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.[20] Consequently, natural killer cell function is better preserved with regional anaesthesia, and metastatic load to the lungs reduced in a rat model of breast cancer metastasis.[15]

When regional and general anaesthesia are combined, the amount of general anaesthetic required is greatly reduced, as is immune suppression presumably. Furthermore, regional analgesia provides superb pain relief, essentially obviating the need for postoperative opioids and consequent adverse effects on immune function and of tumour growth.[17,20] Regional analgesia also reduces the release of endogenous opioids.[21]

Thus, available data suggest that regional anaesthesia and analgesia help to preserve effective defenses against tumour progression by attenuating the surgical stress response, by reducing general anaesthesia requirements and by sparing postoperative opioids.[22] Animal studies are consistent with this theory, showing that regional anaesthesia and optimum postoperative analgesia independently reduce the metastatic burden in animals inoculated with breast adenocarcinoma cells.[23] Available human data, although extremely limited, are also consistent with this theory. For example, paravertebral anaesthesia and analgesia for breast cancer surgery are associated with an approximate fourfold reduced risk of recurrence or metastasis.[24] Similarly, epidural analgesia for radical prostate surgery is associated with a 60% reduction in recurrence risk.[25] Major prospective trials on paravertebral analgesia for breast cancer surgery (NCT00418457)[26] and epidural analgesia for colon cancer are in progress (NCT00684229).

References

1. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005;100(1):4-10.
2. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med. 1996;335(23):1713-1720.
3. Kurz A, Sessler DI, Lenhardt RA. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. 1996;334(14):1209-1215.
4. 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(9285):876-880.
5. Greif R, Akça O, Horn E-P, et al. Supplemental perioperative oxygen to reduce the incidence of surgical wound infection. N Engl J Med. 2000;342(3):161-167.
6. Belda FJ, Aguilera L, Garcia de la Asuncion J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA. 2005;294(16):2035-2042.
7. Benhaim P, Hunt TK. Natural resistance to infection: Leukocyte functions. J Burn Care Rehabil. 1992;13(2 Pt 2):287-292.
8. Jonsson K, Hunt TK, Mathes SJ. Oxygen as an isolated variable influences resistance to infection. Ann Surg. 1988;208(6):783-787.
9. Sheffield CW, Sessler DI, Hopf HW, et al. Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. Wound Rep Reg. 1997;4:339-345.
10. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg. 1997;132(9):997-1004.
11. Kabon B, Fleischmann E, Treschan T, et al. Thoracic epidural anesthesia increases tissue oxygenation during major abdominal surgery. Anesth Analg. 2003;97(6):1812-1817.
12. Akça O, Melischek M, Scheck T, et al. Postoperative pain and subcutaneous oxygen tension. Lancet. 1999;354(9172): 41-42.
13. Denis MG, Lipart C, Leborgne J, et al. Detection of disseminated tumor cells in peripheral blood of colorectal cancer patients. Int J Cancer. 1997;74(5):540-544.
14. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against

postoperative immunosuppression: could they reduce recurrence rates in oncological patients? Ann Surg Oncol. 2003;10(8):972-992.

15. Bar-Yosef S, Melamed R, Page GG, et al. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology. 2001;94(6):1066-1073.
16. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer. 2006;6(3):240-248.
17. Sacerdote P, Bianchi M, Gaspani L, et al. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. Anesth Analg. 2000;90(6):1411-1414.
18. Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 2002;62(15):4491-4498.
19. Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G. Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. Int J Cancer. 1999;80(6):880-888.
20. O'Riain SC, Buggy DJ, Kerin MJ, et al. Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. Anesth Analg. 2005;100(1):244-249.
21. Chae BK, Lee HW, Sun K, et al. The effect of combined epidural and light general anesthesia on stress hormones in open heart surgery patients. Surg Today. 1998;28(7):727-731.
22. Sessler DI. Does regional analgesia reduce the risk of cancer recurrence? A hypothesis. Eur J Cancer Prev. 2008;17(3):269-272.
23. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain. 2001;90(1-2):191-199.
24. Exadaktylos A, Buggy DJ, Moriarty DC, et al. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology. 2006;105(4)4:660-664.
25. Biki B, Mascha E, Moriarty DC, et al. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology. 2008;109(2):180-187.
26. Sessler DI, Ben-Eliyahu S, Mascha EJ, et al. Can regional analgesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. Contemp Clin Trials. 2008;29(4):517-526.