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

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 two5 or six6 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 oxygen8 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 normothermia9 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 block11 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. Whether this minimal residual disease results in clinical metastases depends largely on the balance between antimesostatic immune activity and the tumour's ability to seed, proliferate and attract new blood vessels.\(^\text{14}\)

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

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.\(^\text{20}\) 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.\(^\text{15}\)

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.\(^\text{17,20}\) Regional analgesia also reduces the release of endogenous opioids.\(^\text{21}\)

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.\(^\text{22}\) 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.\(^\text{23}\) 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.\(^\text{24}\) Similarly, epidural analgesia for radical prostate surgery is associated with a 60% reduction in recurrence risk.\(^\text{25}\) Major prospective trials on paravertebral analgesia for breast cancer surgery (NCT00418457)\(^\text{26}\) and epidural analgesia for colon cancer are in progress (NCT00684229).

References

14. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against...