

EDITORIAL VIEWS

Anesthesiology
1996; 84:1-2
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Lippincott-Raven Publishers

Cardiac Outcomes after Regional or General Anesthesia

Do We Have the Answer?

How does one decide when there have been enough studies on a particular topic, such as whether general or regional anesthesia is safer in patients undergoing lower extremity vascular surgery? In this issue of ANESTHESIOLOGY, Bode *et al.*¹ present data from the largest randomized clinical trial in this area; once again, they have found no difference between the different types of anesthesia in perioperative cardiac morbidity and mortality, albeit in a study that admittedly lacked power to find a small difference. Is additional research needed in this area?

There are potential physiologic gains from regional anesthesia in patients undergoing vascular surgery, including modifying the cardiovascular and metabolic stress response to surgery,^{2,3} diminished postoperative hypercoagulability,⁴ and decreased postoperative respiratory depression⁵ when compared with general anesthesia. Although these may reduce perioperative cardiac ischemia, infarction, and death, demonstrating such reductions has been difficult. Before the current study by Bode *et al.*, there were three randomized controlled trials of this issue. The first trial, by Cook *et al.*, randomly assigned 101 patients presenting for lower extremity revascularization to either spinal anesthesia or general anesthesia.⁶ Although they found differences in intraoperative hemodynamic parameters, such as a greater incidence of hypotension in the spinal anesthesia group, they found no significant differences in in-hospital mortality (2% *vs.* 6%) or nonfatal myocardial infarction (2% *vs.* 2%). Christopherson *et al.* and the Perioperative Ischemia Randomized Anesthesia Trial Study Group randomly assigned 100 patients undergoing elective lower extremity revascularization to epidural anesthesia or general anesthesia.⁷ They reported no significant differences in 6-month mortality (8% *vs.* 6%), cardiac-related mortality (2% *vs.* 2%), nonfatal myocardial infarction (4% *vs.* 4%), or unstable

angina (0% *vs.* 4%). The trial was terminated early because of a more than fivefold increased rate of graft failure in the general anesthesia group. The third trial studied 19 patients undergoing femoral-popliteal bypass surgery randomly assigned to epidural anesthesia or general anesthesia; as would be expected in such a small number of subjects, there was no difference between the groups in the outcome of early postoperative ischemic electrocardiographic changes.⁸ There also was a nonrandomized cohort study in 174 patients undergoing infrainguinal arterial bypass surgery, which found no difference in 30-day mortality, nonfatal myocardial infarction, or reversible cardiac events comparing patients who received epidural anesthesia or general anesthesia.⁹

The study by Bode *et al.*¹ attempts to overcome some of the problems with previous research by recruiting a larger number of subjects (more than had been included in all the previous trials) and by including epidural, spinal, and general anesthesia in the same study. The investigators randomly assigned 423 patients scheduled for elective femoral-distal vessel bypass surgery to one of those three anesthetic regimens. Using an intent to treat analysis, they report no statistically significant differences between the groups with regard to in-hospital mortality (epidural anesthesia 3.4%, spinal anesthesia 2.9%, general anesthesia 2.9%; $P = 0.97$), nonfatal myocardial infarction (epidural anesthesia 4.7%, spinal anesthesia 5.2%, general anesthesia 3.6%; $P = 0.82$), angina (epidural anesthesia 6.7%, spinal anesthesia 10.3%, general anesthesia 7.3%; $P = 0.49$), and congestive heart failure (epidural anesthesia 8.7%, spinal anesthesia 10.3%, general anesthesia 8.7%; $P = 0.87$). An interim analysis led to an early termination of the trial when it became clear to the investigators and their data monitoring board that, because the event rates were low and similar in the three groups, they would be unlikely to enroll enough patients to demonstrate any differences.

How should we interpret the current and previous studies of this topic? First, despite studying patients at high risk of perioperative cardiac events, the risks of

Submitted for publication October 6, 1995. Accepted for publication October 16, 1995.

Key words: Anesthesia: general; regional. Cardiac. Morbidity. Vascular surgery.

short-term cardiac mortality and of nonfatal myocardial infarction are relatively low (2–6%), regardless of the choice of anesthesia. In part, this may be an artifact of the randomized controlled trial, because patients in such trials tend to be healthier, or at least, less sick, than those who do not enroll. With such low risks of adverse cardiac outcomes, demonstrating a difference between anesthesia regimens—which are likely to have only modest effects on events happening in the perioperative period—is difficult.

Second, despite the anticipated, and in some instances, demonstrated, pathophysiologic advantages of regional anesthesia, there have been no statistically significant differences in cardiac endpoints. Pooling the results of the four randomized trials in an informal metaanalysis suggests that the difference between regional and general anesthesia, if any, is small. (While the studies differed in important ways, such as using different anesthesia regimens and different definitions of adverse outcomes, the overall results are similar enough that pooling their results seems reasonable.)¹⁰ For in-hospital or short-term cardiac mortality, the best estimate is that there is no difference between regional and general anesthesia, with a 95% confidence limit from –3% to +3%. For the combined outcome of any cardiac event (most of which were self-limited) or death, the best estimate is a 1.5% benefit with general anesthesia, with 95% confidence interval from –4% to 7%. Including the results of the cohort study does not change these estimates appreciably (the confidence limits are somewhat narrower, because there are more patients), nor does comparing either epidural anesthesia or spinal anesthesia alone with general anesthesia (except that the confidence limits become wider).

Thus, although a study with a much larger sample size may find a statistically significant difference in cardiac outcomes related to anesthesia type, it is unlikely to find a clinically significant difference. This basic principle supports Bode *et al.*'s decision to terminate their study early. Although one can bemoan the resulting lack of power in order to dismiss this "negative" study, the most likely explanation for the negative results is that there really is no clinically relevant difference between regional and general anesthesia in terms of the risk of adverse cardiac outcomes. Whether regional, or perhaps just epidural, anesthesia reduces the risk of graft failure is less certain: Bode *et al.* should tell us what happened in their study, and there is still

a role for well done case-control studies to support or refute the Perioperative Ischemia Randomized Anesthesia Trial Study Group results suggesting that type of anesthesia affects graft patency. Additional randomized controlled trials comparing regional and general anesthesia to determine their effects on perioperative cardiac morbidity and mortality are unlikely to be useful. As of now, further trials are not needed.

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Alan S. Go, M.D.

Warren S. Browner, M.D. M.P.H.

General Internal Medicine
San Francisco Veterans Affairs Medical Center
4150 Clement Street
San Francisco, California 94121