How Can We Demonstrate that New Developments in Anesthesia Are of Real Clinical Importance?

To the Editor: — Recently, in their editorial discussion of the paper by Bode et al.,1 Go and Browner2 concluded that additional randomized controlled trials comparing regional and general anesthesia are unlikely to be useful. However, even though surgery and anesthesia are much safer now than 50 years ago, this is no reason to conclude that further significant improvements cannot be made. The problem is how to identify which new developments in anesthesia (and surgery) are of clinical importance. The commentary from Go and Browner does ask two key questions in this regard, namely, the extent to which one can rely on the evidence provided by clinical studies and the extent to which one can generalize from studies performed in one field of surgical and anesthetic practice to other fields.

Individual Trials

It is not appreciated widely just how large randomized clinical trials need to be to detect reliably moderate, but important, differences between treatments.3 For example, Bode et al. state that their study sought to evaluate whether the type of anesthesia has an important influence on perioperative cardiac outcomes in patients undergoing peripheral vascular surgery.4 However, with an overall mortality rate of just 3.1% in their cohort of 423 patients, they would actually have needed more than 24,000 patients to have an 80% chance of detecting even a 50% reduction in mortality rate. Thus, they rightly acknowledge the inability of their own experiment to answer the question they had posed.

This highlights the major dilemma facing any researcher seeking to evaluate whether changing anesthetic techniques can change patient outcomes. Major surgery for “high-risk” patients is now remarkably safe based on the rates of major complications in studies such as that of Bode et al.1 This has important implications for the design of randomized controlled trials to evaluate the impact of any aspect of anesthetic technique on morbidity and mortality rates. As Yusuf et al.5 noted, if a large benefit was associated with a particular clinical maneuver that had been widely used for many years, the evidence for this benefit would be clear, and this would be widely agreed and accepted by clinicians. However, many clinical maneuvers will differ only moderately, and we agree with Go and Browner that the effect of epidural block on surgical outcome is likely to be moderate. Such effects can be important from a clinical and an economic perspective,6 but they will not be detected reliably without large randomized trials.

A second point is a consequence of the low morbidity rate in unselected patients. To have the necessary statistical power to avoid the false conclusion of no benefit, a study should either be extremely large, or it should selectively recruit patients at high risk of complications. Both strategies require a multicenter approach to enroll sufficient patients in a reasonable time, but the selective strategy requires a trial of more achievable size. The Bode et al. study1 can be used to illustrate this. For the sake of simplicity of calculation, we have rounded their observed overall mortality rate from 3.1% to 3% and assumed that each 100 of their patients could be divided into a high-risk group of 10 and a low-risk group of 90 with mortality risks as given in Table 1.

We also can estimate, similarly, cardiovascular morbidity from their results, as presented in Table 2. In the high-risk group, a trial of 945 patients per treatment group would be needed to have an 80% chance of detecting a decrease in mortality rate from 20% to 15%. By concentrating on patients at high risk, trials of modest size (1,890) rather than enormous size (>24,000) are required to have a reasonable chance of identifying modifications to anesthetic and analgesic techniques that could substantially improve outcome for all patients. This assumes that the results in the high-risk group also would be found in the low-risk group. Although we would not expect the benefit to be exactly the same in both groups, there is no good reason to believe that one group would benefit and one would not. We would expect that if there was a benefit, it would exist for both groups, but it may be different in each group.

Such moderate improvements are worthwhile clinically and may be cost-effective if the new or alternative techniques cost no more, or only a little more, than those presently in use. However, to be reasonably sure of identifying benefits of this magnitude in a trial of manageable size and duration, a multicenter study will be required because no single institution is likely to have a sufficient number of high-risk patients.

In practical terms, if 10% of the patients seen by Bode et al. were at high risk and if a new multicenter study could maintain their recruitment fraction of 60%, 11 institutions of the size of the New England Deaconess Hospital could complete the study outlined previously in the same time as Bode et al. took to accrue 423 unselected patients. This goal is realistic and achievable.

Table 1.

<table>
<thead>
<tr>
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<th>High-risk Group</th>
<th>Low-risk Group</th>
<th>Total (unselected patients)</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Operative mortality (%)</td>
<td>20</td>
<td>0.9</td>
<td>3</td>
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Generalizing from Individual Studies

Bode et al.1 studied cardiac outcomes in patients undergoing peripheral vascular surgery. This represents a narrow focus of outcomes.
in a specific, but nevertheless important, group of patients. They also studied intraoperative epidural block only and excluded postoperative epidural analgesia. It is recognized that first, postoperative epidural analgesia may be more important than intraoperative epidural block in improving outcome, and secondly, patients having peripheral vascular surgery in the lower limbs do not experience the same intensity of postoperative pain (or surgical traumatic stress) as patients having major abdominal aortic procedures.3,6,8,11 These observations suggest that the conclusions of Go and Browner may have little validity outside of the field of peripheral vascular surgery.10,11 Their opinion should not be extended uncritically beyond the narrow confines of the investigation by Bode et al9 to the larger pool of patients at high risk of complications. In such patients, there already is some evidence that in the setting of complex surgery, epidural block may reduce the incidence of adverse events.8,6,8,11 Recent correspondence concerning the report of Bode et al. supports our view of the importance of postoperative epidural block in improving outcome and not extending their conclusions to the narrow subset of patients they studied.10,11

There are three other reasons to question the conclusions of Go and Browner. First, the totality of evidence that they present is small, a much larger body of research was needed to provide convincing evidence for the important, but moderate, clinical benefits of Tamoxifen in the management of breast cancer.12 and thrombolytic therapy after myocardial infarction.13,14 Secondly, it is based solely on published trials, and the addition of any unpublished trials that may exist may lead to different conclusions.9 Thirdly, and most importantly, the evidence cited by Go and Browner10-16 actually indicates the existence of genuine uncertainty about the merits or otherwise of epidural block and, therefore, represents a strong argument for an adequately sized, multicenter randomized trial in high-risk patients. This view also is supported by recent correspondence.10,11 The conclusion that no further trials are needed is premature, and this is well illustrated by an evaluation of a series of trials reporting the effects of long-term beta blockade.15 Twenty-one of 24 randomized trials failed to achieve conventional levels of significance because each was too small on its own. Reliable assessment of moderate effects (15-20% improvement in the outcome of myocardial infarction) attributable to beta blockade required randomization of 10,000-20,000 patients with a good prognosis or a somewhat smaller study of patients with a poor prognosis.15 The important consideration in the number of randomized patients needed is not the number of patients, but rather the number and rate of the outcomes to be analyzed.

Conclusions

Improvements in anesthetic and surgical techniques that already have occurred mean that any improvement from a single future develop-

Table 2.

<table>
<thead>
<tr>
<th>Condition</th>
<th>High-risk Group (%)</th>
<th>Low-risk Group (%)</th>
<th>Total (unselected patients, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (40)</td>
<td>2 (18)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Angina</td>
<td>6 (60)</td>
<td>3 (27)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (60)</td>
<td>3 (27)</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>

References


13. Fibrinolytic Therapy Trialists’ Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1,000 patients. Lancet 1994; 343:311–22


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In Reply—Dr. Rigg et al. suggest that the relatively low cardiac morbidity and mortality observed in the study by Bode et al. reflects the case mix of patients in that study. They hypothesize that studying only high-risk patients would generate a more accurate estimate of the effect of anesthesia choice on cardiac outcome.

To the extent that randomized controlled trials enroll less ill patients than are typically seen among the total surgical population, the low event rates seen in such studies may be partially an artifact. However, patients undergoing lower extremity vascular surgery, including those enrolled in trials, are already high-risk. It is not at all clear how Rigg et al. would subclassify such patients into ‘high’ high-risk and ‘low’ high-risk, nor do they provide a source for these estimated event rates. And would patients at high high-risk, even if they could be identified, undergo elective vascular surgery? Most physicians would consider an expected perioperative mortality of 20% to be prohibitively great. A study enrolling such patients may never take place. Finally, there is little, if any, reason to believe that intraoperative anesthesia choice would reduce perioperative mortality rate, which has variety of causes by 25%.

Our review and informal meta-analysis were performed on published trials, weighted appropriately for sample size. Because publication bias generally favors the publication of trials with positive results, inclusion of unpublished trials generally leads to a reduction in the summary effect size, not the converse. Similarly, although most of the trials had relatively few patients, small published trials generally overestimate the effect of a treatment. Although these potential biases would favor detecting a beneficial effect of regional anesthesia compared with general anesthesia, no significant benefit was found: 0% (95% CI, −3% to +3%) difference for in-hospital or short-term cardiac mortality and 1.5% (95% CI, −4% to +7%) difference for any cardiac event or death favoring general anesthesia.

Despite the potential physiologic advantages from regional anesthesia compared with general anesthesia in patients undergoing vascular surgery, there has been no demonstrated statistical and more importantly, clinical benefit on cardiac outcomes. There may, however, be other reasons to prefer one of the techniques. Nor does the lack of benefit mean that additional research in reducing perioperative cardiac morbidity and mortality is futile. Other strategies, such as those addressing the management of postoperative pain or periprosthetic myocardial ischemia, are promising. As to further trials comparing the effects of currently available techniques of regional and general anesthesia on cardiac outcome, our conclusion still stands: none are needed.

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