

When It Comes to Outcome, We Need to Define What a Perioperative Epidural Technique Is

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After reading the results of the MASTER study (1) and the Veterans Affairs cooperative study (2), as well as those of the study by Peyton et al. (3) published in this issue of *Anesthesia & Analgesia*, anesthesiologists who believe that perioperative epidural techniques have decreased the incidence of perioperative cardiopulmonary complications may be confused. It would appear that even in a high-risk population analysis performed for this publication (3), perioperative epidural analgesia was not superior to general anesthesia/parenteral analgesia in reducing the incidence of pulmonary, cardiac, and infectious complications. Thus, the results from recent meta-analysis studies (4–6) are not reproduced in these large randomized clinical trials (RCT). What can be happening?

There are three important issues that need to be addressed before accepting the conclusions of this (3) and the other two above-mentioned reports (1,2). Thus, we will make comments in three areas: protocol design, evolution and timeliness in research, and statistical design of the study.

Protocol Design

The study by Peyton et al. (3) is a subset analysis of data previously published reporting the results of a multicenter trial (1). Careful assessment of the treatment protocol in this study (1) reveals that there may be a problem with study design. The protocol for epidural treatment in the MASTER study is not defined either in the original publication (1) or in the publication in which the protocol treatments should have been described (7). Major questions with the protocol design that cast doubt in the results of this and the “parent” study include the following.

1. Did patients have a thoracic epidural placed according to the site of surgery, i.e., T6-7 or T7-8 for upper abdominal procedures and T4-5 or T5-6 for the thoracic procedures?
2. Did they receive an intraoperative local anesthetic, and, if this occurred, was the administration continuous throughout the surgery?
3. Were there limits in the doses of inhaled anesthetics and IV opioids set for the intraoperative period to force the managing physicians into using an appropriate concentration and volume of an intraoperative local anesthetic?
4. What measures were taken to guarantee that the epidural catheter was indeed in the epidural space both during surgery and throughout the postoperative period?
5. Was a local anesthetic/opioid mixture used for postoperative analgesia, and was it used continuously throughout the study period?
6. How were uncontrolled pain and breakthrough pain defined and treated in the epidural group?
7. At what point during the day and how often was pain measured?
8. Did patients in the epidural group receive IV opioids, nonsteroidal antiinflammatory drugs, or both for the treatment of incidental/breakthrough pain? If so, how much?
9. Did the protocol determine criteria for extubation, and were patients extubated when they reached these criteria?
10. Did the protocol establish criteria for discharge from the intensive care unit and the hospital?

Although the authors argue that they designed the study to allow flexibility to practitioners so that the conditions of the study would resemble everyday clinical practice, the cardiopulmonary changes occurring in the perioperative period, leading to morbidity and mortality events, does not allow for that flexibility. This is because there are specific pathophysiologic changes that lead to dysfunction, morbidity, and death, and these changes need to be controlled in a specific manner when a thoracic epidural technique is used. Thus, the answers to the questions formulated above are of critical importance. The other recently

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published large outcome study (2) is a good template for illustrating some of these concerns. Patients undergoing abdominal surgery were treated with either lumbar or thoracic epidural catheters, and the results section does not tell us if the number of lumbar catheters was more than the number of thoracic catheters or *vice versa*. The local anesthetic re-dosing schedule was 5–10 mL every 3–5 h. Thus, there is no guarantee that patients had a complete sensory block throughout surgery. Moreover, only opioids were used for postoperative analgesia, in the form of an intermittent bolus. In this study (2), “patients were considered to have had epidural anesthesia technique if they received any epidural local anesthetics or opioids.” If this was the case in the MASTER study (1), the basic principles of an epidural technique designed to improve pulmonary and cardiac outcome were not fulfilled. Additionally, if the concentration of the inhaled anesthetic was larger than 0.5 minimum alveolar anesthetic concentration and there was a frequent use of IV opioids during the course of surgery, the study is not comparing an epidural technique with general anesthesia but two general anesthetic techniques, with one group having an epidural catheter inserted. Similarly, if patients received epidural opioids alone and/or significant amounts of IV opioids or other analgesics for the treatment of uncontrolled or breakthrough pain, as opposed to epidural patient-controlled analgesia, again, the study is not comparing the results of epidural versus parenteral analgesia. This information should have been reported in the results section so that the reader could make an evaluation as to how much the epidural solution contributed to the anesthetic and analgesic plan.

The importance and ramifications underlying these issues regarding postoperative outcome have been addressed previously (8,9). In short, an epidural local anesthetic is essential to improve pulmonary, cardiac, and gastrointestinal outcome. Pulmonary and cardiac morbidity will prolong intensive care unit and hospital stay. Gastrointestinal dysfunction (ileus) will affect the length of hospital stay. The effects that the local anesthetic, but not the opioids, have in returning the functional residual capacity/closing capacity proportion back to normal (4,10,11) will have direct implications in the length of postoperative mechanical ventilation, because it directly affects the development of atelectasis, the increase in shunt fraction, hypoxemia, and the need to reintubate the trachea and ventilate patients. Likewise, the incidence of pulmonary infections is proportional to the length of tracheal intubation and mechanical ventilation. Epidurally administered local anesthetics appeared to produce their beneficial effects in pulmonary outcome by promoting the postoperative recovery of diaphragmatic contractility (12,13).

The effects of the neuroendocrine response and a sympathetic blockade on the coronary artery tone of patients with severe atherosclerotic heart disease (AHD) undergoing noncardiac surgery have also been discussed (14). In short, the activation of the neuroendocrine response results in high levels of norepinephrine that stimulate coronary endothelial production of nitric oxide, resulting in paradoxical vasoconstriction (vasospasm) in patients with AHD (15,16). Thus, for a patient to derive a full protective cardiac effect from a perioperative epidural technique, the catheter must be inserted in the high thoracic region. Moreover, a local anesthetic must be administered both during and after surgery (inhibition of intraoperative neuroendocrine response and sympathetic blockade), in a continuous fashion, and for at least 72 h. In fact, the beneficial effects of local anesthetic administration through a high thoracic epidural catheter in patients with severe symptomatic AHD who are not candidates for surgical revascularization have been documented (17,18). Likewise, angina pectoris unresponsive to therapy with IV nitroglycerin, calcium channel blockers, β -adrenergic receptor blockers, and aspirin has been successfully treated with high thoracic epidural administration of a local anesthetic (19). Clearly, no one has ever considered treating these severely ill patients with opioids only, administered through a lumbar epidural catheter.

Evolution and Timeliness in Research

I agree with Peyton et al.’s (3) observation that positive findings from a metaanalysis should be confirmed by a large RCT. However, as illustrated previously, controlling all the variables in large-scale, multicenter studies of this nature is far more difficult than doing so in large RCTs evaluating the treatment of hypertension, osteoarthritis, myocardial infarction, and so on. This is because the therapeutic options in these studies involve only taking or not a pill or administering or not administering an IV drug. This is not so with an epidural outcome study. Moreover, it is important to recognize that problems considered crucial 10 yr ago may not have the same importance now. For example, perioperative myocardial ischemia and myocardial infarctions were recognized as a critical problem in the 1980s and early 1990s. Thus, the focus of several studies at that time was on finding techniques that would reduce their incidence. However, according to the Agency for Healthcare Research and Quality, a number of RCTs support the perioperative use of β -blockers to reduce the morbidity and mortality associated with noncardiac surgery in patients at risk for cardiac complications (20). Thus, it would appear that, at this juncture, cardiac outcome may be improved by

either appropriately implementing epidural techniques that decrease the intraoperative neuroendocrine response and produce a sympathectomy from T1 to T5 throughout the perioperative period or by administering perioperative β -blockers. The focus of postoperative outcome research now has been shifted to hasten recovery of gastrointestinal function (21,22), as an important component of shorter hospital stays, and to decrease postoperative fatigue syndrome.

Statistical Design

Peyton et al.'s study (3) is a retrospective subset analysis of data collected in a prospective manner under a larger trial (1). Subsets of high-risk patients were defined. Within these patient groups, comparisons were made for several end-points of postoperative complications between those who received epidural analgesia and those in a control group. The results from the statistical analyses for these comparisons are summarized in table 1 of the study (3). There are several statistical issues with regard to these analyses. First, no statistical correction was made for multiple testing, thereby causing an inflated Type I error rate. Within each end-point, a Bonferroni-adjusted P value would have set a significance level of 0.01. With use of this stricter criterion to control for Type I error, there would not have been any significant differences between types of analgesia for the subgroups compared. Also, it is not stated whether there was an overlap of patients among the defined end-points. For example, were there patients with pneumonia who also experienced respiratory failure? If so, then it is not clear how the results should be interpreted. Another observation is that there is an overlap between criteria for subgroup stratification (i.e., arterial partial pressure of oxygen (P_{aO_2}) <50 mm Hg vs >50 mm Hg) and end-point measurement. It appears that either the subgroup stratification or the end-point definition was *ad hoc*. If the subgroup was derived with knowledge of the outcome, then the results from such an analysis are biased and therefore not meaningful. Similarly, if the end-point was derived with a knowledge of differences between subsets of patients, the results from the analysis are also highly suspect. As stated in *Clinical Trials: A Methodologic Perspective*, "As a general rule, the same data should not be used to both generate a new hypothesis and to test for it. Apart from the statistical pitfalls, investigators must guard against forcing the data to fit the hypotheses. . ." (23).

With regard to the statistical analyses shown in table 2, both mean and median tests were performed for the comparisons (3). One test to compare the measure of center between distributions is sufficient. Because the data were not normally distributed, either a

nonparametric test or normalization of the data followed by use of a Student's t -test would be appropriate to analyze the data. Also, showing the mean and standard deviation in the original units, as opposed to the log-transformed units, would give the reader a clearer and more easily understood interpretation of the results.

As a final comment, the results from the analysis of the early epidural failure subgroup are not discussed in the article.

In conclusion, there appear to be contradictory findings in the results of recent large-scale outcome studies compared with those obtained via metaanalysis. Concerns in the design and execution in all of these studies prevent the conclusion that perioperative epidural techniques should be disregarded as a means to decrease perioperative cardiopulmonary and infectious complications. These limitations in study design are yet another reminder to all of us that the conclusion section in an article should start by stating, "Under the conditions of the present protocol design. . ." and so on. In short, do not throw away those Tuohy needles and epidural catheters just yet.

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