 

# *Primary* versus *Secondary Outcomes in Gargantuan Studies*

EPIDURAL analgesia is currently the most effective method available to treat pain in labor. Retrospective studies conducted during the 1980s and 1990s suggested that epidural analgesia might slow the progress of labor and cause unnecessary Cesarean sections.[1] Unfortunately, retrospective study cannot readily separate cause and effect. If patients with slower labor are more likely to receive epidural anesthesia, then a retrospective study may identify an association between epidural anesthesia and slowed labor, but it does not establish a causal link.

Causality is only established by a prospective, double-blind, randomized trial. Unless there is a failure of blinding or randomization, all confounding variables (*e.g.*, slower labor on enrollment into the trial), including the "unknown unknowns," are evenly divided between the treatment groups. A difference in outcome can only be explained by the difference in treatments, establishing causality. Thus, recent randomized prospective studies[2,3] have dispelled the notion that early initiation of epidural anesthesia increases in the risk of Cesarean section. The question remains, however, how early can an epidural be placed without enhancing the risk of Cesarean delivery. In this issue of ANESTHESIOLOGY, Wang *et al.* definitively address this question in the largest randomized, prospective clinical trial of labor epidural ever conducted at a single center.[4]

The authors randomly assigned 12,793 nulliparous women who requested analgesia at 1-cm cervical dilation or less to receive an "early epidural" when they reached 1-cm dilation or a "late epidural" after 4-cm cervical dilation. The women were treated with meperidine until the assigned cervical dilation was reached. The primary outcome variable, the rate of Cesarean delivery, did not differ between the groups. The time from randomization (at first request for analgesia) to delivery was not different. Lastly, there was no increase in the rate of instrumental vaginal delivery. The large size, prospective randomized design, and unambiguous outcome measures definitively demonstrate that there is no clinically important relationship between epidural anesthesia given as early as 1-cm cervical dilation and (1) Cesarean delivery, (2) labor duration, and (3) rate of instrumentation. As such, the safe period for epidural analgesia has now been pushed back to 1-cm dilation.

Bigger is not always better though. Every study entails risk. In this case withholding epidurals created the risk of lower satisfaction. The authors state that they designed their study to be able to detect a difference in the rate of Cesarean section of 2.3%. It is arguable whether this is a reasonable difference to target. In this case, the authors anticipated proving the null hypothesis. This trial should have been designed to prove "noninferiority" within a reasonable confidence interval.

The authors measured 29 secondary outcomes. The interpretation of statistically significant secondary outcomes can be complex, particularly when the primary outcome does not demonstrate statistical significance, as in this case.[5,6] A trial this large may detect relatively small difference in secondary outcomes that are clinically trivial or even spurious. For example, the authors followed up with the patients 6 weeks after delivery on breastfeeding success. Early epidural was strongly associated with less success with breastfeeding ($P < 0.0001$). Despite the strength of the statistical association, the difference between the two groups was modest (70% success in the early epidural group compared to 78% success in the late epidural group). The physiologic mechanism for breastfeeding problems caused by the difference between 4.8 and 12.6 h of exposure to epidural ropivacaine and sufentanil is difficult to imagine. It is difficult to interpret multiple secondary endpoints in a randomized clinical trial; despite the very low *P* value, this finding should be considered a novel hypothesis generated by this study that requires further follow-up as a primary endpoint in a subsequent randomized controlled trial. The authors have undertaken this exercise, and their findings are sure to be important.

There are several additional anomalies among the secondary endpoints. For example, the Visual Analog Scale scores in patients receiving an epidural at 1 cm were similar to those in women receiving opioids until the epidural was placed at 4 cm. This seems surprising; a properly functioning epidural should be almost completely effective at blocking labor pain. Although the Visual Analog Scale scores were similar, maternal satisfaction was significantly higher in the early epidural group (84 *vs.* 62, $P < 0.01$). Perhaps the difference in maternal satisfaction was the result of a true difference in pain that was obscured by intersubject variability, or perhaps the difference was the result of

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increased likelihood of nausea and vomiting in the late epidural group.

Other groups have found an increased incidence of maternal fever related to epidural analgesia.[7] In the study by Wang *et al.*, earlier epidural placement was not a risk factor for maternal fever. The authors found no difference in maternal temperature between groups or any difference in the incidence of neonatal sepsis work-ups.

Prospective randomized trials of this size are not common in our specialty. The study by Wang *et al.* illustrates both the strength and potential weaknesses of such studies. The strength is that the primary endpoint can be established with great certainty, permitting as assessment of causality. The disadvantage is that for (very unintuitive) statistical reasons, there is a risk of spurious associations being identified among the secondary endpoints. The conservative view is to accept the primary endpoints as definitive and view any associations seen with the secondary endpoints with caution, particularly if a causative mechanism is not evident.

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