Bispectral Index *versus* Minimum Alveolar Concentration for Prevention of Intraoperative Awareness

Does a Practical Controlled Trial Provide CERtainty?

APPROXIMATELY half of all medical care provided in the United States is based on insufficient scientific evidence and may even be of "uncertain or questionable value."[1] This realization has spurred interest and extensive government funding in comparative effectiveness research (CER) with the ultimate goal to improve the effectiveness, efficacy, and efficiency of health care. To date, few initiatives to conduct and publish studies guided by principles of CER in perioperative medicine, and specifically in the field of anesthesiology, have been taken. In this issue of ANESTHESIOLOGY, Mashour *et al.*[2] present a major leap forward in this endeavor to participate in CER and highlight the importance that our specialty can play in answering difficult clinical questions, which will hopefully convince stakeholders to fund more such initiatives.

"… the critical component of both monitoring strategies [to reduce awareness during surgery] may well be the use of an automated monitor alert system to enhance vigilance and improve human performance."

Multiple studies have already investigated whether bispectral index spectroscopy (BIS) monitoring reduces risk of intraoperative awareness. The authors of this study were unable to find differences in the incidence of awareness or variables of recovery in a randomized trial with more than 18,000 patients when comparing monitoring protocols based on BIS values or anesthetic concentration. By *post hoc* analysis, the protocol based on BIS monitoring reduced the incidence of definite or possible intraoperative awareness compared with routine care.[2] This study is of particular interest for two reasons. As recently pointed out in an editorial by Devereaux *et al.*,[3] studies of this large size are required to study low-incidence outcomes with sufficient confidence in the statistical significance of results. In addition, this protocol incorporated the high standards demanded for CER, including the assessment of effectiveness, efficacy, and efficiency. First, they performed their study in a large, "real world" patient population in various hospitals undergoing various procedures, thus affording their results a high level of external validity. Second, they compared the impact of various competing strategies on various outcomes, which is in contrast to the typical standard that compares only controls (*e.g.*, placebo) with the intervention for a single outcome. Finally, they assessed economically important outcomes (*e.g.*, recovery variables) to put the outcomes into a wider context.

Performance of CER has specific components outlined by the Federal Coordinating Council for CER that focus on the need for the evolution of research methodology.* Traditional "Gold Standard" clinical study designs, such as randomized controlled trials, may pose limitations (*e.g.*, low external validity of results because of strict protocols and study environments) to the ability of researchers to answer important CER questions. In response, various groups have proposed new approaches,[4] such as practical controlled trials that compare clinically relevant alternative interventions, select diverse populations for study, utilize diverse practice settings, and evaluate a wide range of outcomes without the constraints of a randomized controlled trial with its strict inclusion and exclusion criteria.[5] Thus, practical controlled trials may be better equipped to address the "real world" questions of interest to decision-makers as proposed by the

Photo illustration: J. P. Rathmell/W. Levine.

Accepted for publication July 2, 2012. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

* www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf. Accessed June 15, 2012.

 Anesthesiology 2012; 117:693–5

◆ This Editorial View accompanies the following article: Mashour GA, Shanks A, Tremper KK, Kheterpal S, Turner CR, Ramachandran SK, Picton P, Schueller C, Morris M, Vandervest J, Lin N, Avidan M: Prevention of intraoperative awareness with explicit recall in an unselected surgical population: A randomized comparative effectiveness trial. ANESTHESIOLOGY 2012; 117:717–25.

definition of CER. In this context, how do previous large-scale prospective trials investigating BIS monitoring and intraoperative awareness compare? The B-aware trial constitutes the traditional randomized controlled trials comparing BIS monitoring with no intervention and reported decreased risk with use of BIS monitoring in a selected, high-risk population. Although this trial certainly contributed to evidence-based practice, it was limited by the lack of generalizability to all patients (*i.e.*, external validity) and the fact that it did not compare BIS with an alternative strategy to decrease the risk of intraoperative awareness.[6] The B-Unaware trial, which compared BIS with minimum alveolar concentration-guided protocols[7] and found no advantage in a high-risk population, addressed the latter shortcoming but not the former. Although this sequence of studies on BIS monitoring represents the evolution toward meeting requirements for CER, the additional cost and effort this progression required to come to the conclusions presented in the current manuscript should not be ignored. This example illustrates the important role that contemporary planning of research methodology needs to play in studies of this magnitude and importance. It must be noted that various task forces have been formed to deal with exactly this topic and identify which study designs are best for answering specific questions in the context of CER. Further, it is important to note that randomized controlled trials and practical controlled trials are not always the best, most timely, and cost-effective way to approach CER-related questions. Meta-secondary database analyses, and even case studies or a collection of research works, all have their legitimate roles.[8]

In the context of CER, it seems that either minimum alveolar concentration- or BIS-based monitoring protocols combined with a sophisticated monitor alert system are similarly effective in reducing risk of intraoperative awareness in the general population when compared with no intervention. Furthermore, within the study context, there was no advantage to the utilization of BIS monitoring for any of the studied clinical outcomes, thus questioning the additional cost incurred by the use of this device. However, as noted by the authors, the critical component of both monitoring strategies may well be the use of an automated monitor alert system to enhance vigilance and improve human performance. These alert systems are not widely in place at this time but are increasingly of clinical interest and viability.[9] A critical feature of automated monitoring alerts is careful selection of alarm values to enhance vigilance without creating alarm fatigue,[10] and further work may be needed to refine these values for BIS and MAC monitoring. Although "smart" monitoring systems may help prioritize alarm information, constant vigilance and development of situation awareness are critical to anticipating and optimizing patient situations and outcomes in a systems-based fashion.[11]

CER represents a major opportunity to institute accountability into the healthcare system, but has limitations. Frequently, no causalities can be established to explain results and provide mechanistic direction for future interventions. In CER, available strategies to prevent a particular outcome are compared, yet a number of patients may still experience an adverse event despite interventions. In this case, approximately 1 in 1,000 patients experienced awareness during anesthesia despite MAC-based or BIS-guided anesthesia. Hence it is of utmost importance to not stop research endeavors in a particular field, because the "big question" appears to have been answered with a study based on a large sample size. Although population-based studies may determine the value of an intervention on a large scale, the impact of low incidence outcomes on the individual remains a concern. The undetermined reason why a subgroup of patients remains prone to awareness during anesthesia, despite interventions to prevent it, gives credence to the continuity of research and a move back from the bedside to the bench. Obvious questions to be addressed include: Can improvements in monitor-alerting technology or human performance to increase situational awareness further decrease risk of intraoperative awareness? Are there potential differences between individuals that may make them more prone to awareness during anesthesia? Although some clinical risk factors for this event have been identified in the past, variables beyond what has been traditionally considered in related research in this field have to be considered. To this point, there is an emerging concept that the brain does not enter an unconscious state in the same way it arises from it (*i.e.*, that it exhibits hysteresis), and that this process may be affected by genetic factors.[12]

In conclusion, the present article is proof that anesthesia-related CER is not only feasible, but can play a major role in shaping accountable and evidence-based perioperative care. To maximize efficiency, it is becoming increasingly important to identify the appropriate study design and match it to desired goals of a particular CER study. One has to caution that even extensive population-based CER trials that define the currently available, most effective, efficacious, and efficient intervention to address a problem, may not yield the optimal intervention for individualized care.

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References

1. Manchikanti L, Falco FJ, Boswell MV, Hirsch JA: Facts, fallacies, and politics of comparative effectiveness research: Part I. Basic considerations. Pain Physician 2010; 13:E23–54
2. Mashour GA, Shanks A, Tremper KK, Kheterpal S, Turner CR, Ramachandran SK, Picton P, Schueller C, Morris M, Vandervest J, Lin N, Avidan M: Prevention of intraoperative awareness with explicit recall in an unselected surgical population: A randomized comparative effectiveness trial. ANESTHESIOLOGY 2012; 117:717–25

3. Devereaux PJ, Chan MT, Eisenach J, Schricker T, Sessler DI: The need for large clinical studies in perioperative medicine. Anesthesiology 2012; 116:1169–75
4. Tunis SR, Benner J, McClellan M: Comparative effectiveness research: Policy context, methods development and research infrastructure. Stat Med 2010; 29:1963–76
5. Tunis SR, Stryer DB, Clancy CM: Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003; 290:1624–32
6. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT: Bispectral index monitoring to prevent awareness during anaesthesia: The B-Aware randomised controlled trial. Lancet 2004; 363:1757–63
7. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, Saager L, Turner MS, Rao S, Bottros M, Hantler C, Jacobsohn E, Evers AS: Anesthesia awareness and the bispectral index. N Engl J Med 2008; 358:1097–108
8. Memtsoudis SG, Besculides MC: Perioperative comparative effectiveness research. Best Pract Res Clin Anaesthesiol 2011; 25:535–47
9. Gamble KH: An eye on safety. With patient safety a top goal, CIOs are embracing wireless monitoring systems that can provide busy clinicians with another set of eyes. Healthc Inform 2009; 26:26, 28–30
10. Graham KC, Cvach M: Monitor alarm fatigue: Standardizing use of physiological monitors and decreasing nuisance alarms. Am J Crit Care 2010; 19:28–34
11. Fioratou E, Flin R, Glavin R, Patey R: Beyond monitoring: Distributed situation awareness in anaesthesia. Br J Anaesth 2010; 105:83–90
12. Friedman EB, Sun Y, Moore JT, Hung HT, Meng QC, Perera P, Joiner WJ, Thomas SA, Eckenhoff RG, Sehgal A, Kelz MB: A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: Evidence for neural inertia. PLoS One 2010; 5:e11903