Beyond the randomized controlled trial

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Advances in surgical techniques and anesthetic care have enabled us to deliver improved surgical outcomes and to operate on sicker patients. As an intrusive, risky, and expensive phase of care, the perioperative period challenges traditional research techniques. In particular, conducting research in the pediatric population has presented significant consent, ethical, and logistical challenges. Overall, much of the surgical outcome and anesthesia safety progress is rooted in process-of-care research. However, many perioperative clinical decisions are based upon anecdote and habit rather than evidence.

The randomized controlled trial (RCT) remains the gold standard of medical research and knowledge creation. Hailed as the only research method capable of providing causal relationship data, RCTs are typically regarded as the highest quality of research in evidence based medicine reviews and practice guidelines. The tight control of care protocols and random allocation of patients is designed to eliminate confounding variables.

Fortunately, significant perioperative adverse events directly attributable to anesthesia have decreased in frequency over the past 50 years. As a result, the study of such events demands large patient populations in order to achieve the statistical power necessary to make causal inferences. Unfortunately, the labor intensive nature of RCT design, conduct, and patient recruitment results in a very high cost per patient enrollment. This often forces RCT to enroll relatively small patient populations or focus on specific high risk populations that will provide increased statistical power. This tension – the need for large datasets to research infrequent events in perioperative medicine versus the small sample size due to cost and logistical constraints of RCT – has resulted in many recent clinical controversies: ß-blockade,

coronary stent anticoagulation management, transfusion triggers, antifibrinolytic therapy, glucose management, and coronary revascularization.

Concurrently, there is increasing awareness that intraoperative hemodynamics, anesthetic choice, fluid resuscitation, blood product administration, pain management, and medication administration may impact perioperative complications such as myocardial infarction, stroke, respiratory depression, acute kidney injury, infection, cancer progression, death, cognitive function, and developmental problems. Data evaluating these relationships are limited to animal models or small studies with a few hundred patients.

In this environment, the research process must expand to incorporate tools that complement the traditional RCT. The use of large observational datasets has now become mainstream in the general medicine and surgical literature. The Foundation for the National Institutes of Health and Food and Drug Administration recently founded the Observational Medical Outcomes Partnership hoping to detect drug safety issues before they become widespread. The Agency for Healthcare Research and Quality has aggressively funded and supported large national registries.

Several national datasets are now available for medical research. The Nationwide Inpatient Sample (NIS) and National Surgical Quality Improvement Program (NSQIP) are de identified publicly available datasets that incorporate detailed comorbidity and procedural data. The Society of Thoracic Surgeons database has exceptionally detailed patient and procedural information for cardiothoracic researches. Each of them has been used to publish important research that has challenged and changed fundamental care patterns. Unfortunately, none of the these datasets has detailed anesthetic information or patient hemodynamic parameters.

This challenge can be addressed by integrating Anesthesia Information Management System (AIMS) data with other sources of risk adjustment and outcome data. Although these modern AIMS have been in existence for more than a decade, there are limited clinical research publications based upon them. The primary research limitation of these systems was the

historical absence of preoperative risk stratification data elements within the AIMS. However, recent AIMS implementations have expanded far beyond the intraoperative record: discrete preoperative comorbidity elements recorded as part of the anesthesia history and physical are now incorporated into many AIMS. The integration of intraoperative AIMS with elements from national surgical subspecialty outcome databases, demographic, billing, laboratory, blood bank, pharmacy, radiology, and national death records can create novel datasets for knowledge creation.

A unique innovation is the use of complementary data sources to identify postoperative outcomes of interest. Although the specialty of anesthesia has historically focused on proximate quality endpoints occurring within 24 hours of an operation, state of the art research must use long-term definitions and data sources. To that end, we have used laboratory, administrative, and billing information system interfaces to identify postoperative in-hospital mortality, serum creatinine, troponin-I, hemoglobin, glucose, renal replacement therapy, and ventilator days. By securely cross-referencing patient identifiers to the Social Security Administration's Death Master File, we have also used long-term all-cause mortality in our analyses.

By incorporating these broad data elements with statistical techniques and expertise specifically designed for large dataset analysis, the effect of confounding variables inherent in observational research can be mitigated. Missing value analysis, data imputation, multivariate modelling techniques, propensity score derivation, covariate adjustment, and population splitting techniques can be used to maximize the potential of large datasets.

However, all research tools and techniques have their limitations and can be misused – large dataset analysis is not immune to this challenge. The most fundamental and concerning challenge of large dataset research is poor data quality. Unfortunately, the concept is not as simplistic as whether a given dataset is high or low quality – within each dataset, specific elements may have high or low data quality, depending on the source of the data (automated versus provider entered) and the consistency of data entry. The researcher must expend

significant effort observing data entry by the point of care clinician to ascertain whether or not it will be an adequate substrate for analysis. The researcher must confirm the quality of the data by sampling and testing the data against an external “gold truth” data source. Most importantly, the researcher must have the self-restraint to acknowledge that certain important questions cannot be addressed using the data source available to them.

In addition, large dataset research demands the same prospective rigor of an RCT: a detailed literature review to identify the current state of knowledge, prospective patient inclusion and exclusion criteria, objective and quantifiable outcomes, collection of as many confounding variables as possible, and prospective definition of a rigorous statistical analysis plan. Large dataset research also provides particular insightful information when applied to specific clinical questions: events with low incidence (< 2 or 3%); situations difficult to randomize, control, or consent (emergency surgery, hypotension, pediatrics); infrequent adverse side effects of treatments; and low frequency or rare treatments.

In summary, large dataset research can be a valuable addition to a broad research toolset. If used correctly to address appropriate questions, it can advance the science of medicine. However, it demands the same rigor and restraint as other traditional knowledge creation methods.

References

1. Sox HC, Greenfield S: Comparative effectiveness research: a report from the institute of medicine. Ann Intern Med 2009; 151: 203-5
2. Sessler DI: Long-term consequences of anesthetic management. Anesthesiology 2009; 111: 1-4
3. Neuman MD, Fleisher LA: Using quality improvement databases to advance medical knowledge: Opportunities and challenges. Anesthesiology 2009; 110: 449-50
4. Li G, Warner M, Lang BH, Huang L, Sun LS: Epidemiology of anesthesia-related mortality in the United States, 1999-2005. Anesthesiology 2009; 110: 759-65
5. Kheterpal S, O'Reilly M, Englesbe MJ, Rosenberg AL, Shanks AM, Zhang L, Rothman ED, Campbell DA, Tremper KK: Preoperative and intraoperative predictors of cardiac adverse events after general, vascular, and urological surgery. Anesthesiology 2009; 110: 58-66
6. Hannenberg AA, Warner MA: The Registry Imperative. Anesthesiology 2009
7. Avorn J: In defense of pharmacoepidemiology--embracing the yin and yang of drug research. N Engl J Med 2007; 357: 2219-21