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Should variation in care drive our clinical trial agenda?

Editorial

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In clinical medicine there is a strong drive to reduce variation of care. Should desires to reduce variation of care drive our clinical trial agenda? In principle, reducing variation in care should be a good thing. Reducing variation can improve outcomes and reduce costs. This is due to: a) reducing error and improving the reliability, speed and skill base as the clinician and hospital follow increasingly familiar care pathways and b) adopting only practices where there is good evidence for better outcomes. The problem is that in many aspects of anesthesia there is not a lot of high quality evidence.[1.] Clinical trials provide high quality evidence and thus the need for evidence to reduce variation would seem to be a good driver for clinical trials. It is however, not that simple.

As an example let's consider what is the optimal maintenance anesthetic for tonsillectomy? In our department practice is cleanly divided between the volatile anesthesia enthusiasts and the total intravenous anesthesia (TIVA) enthusiasts. The TIVA versus volatile debate is well recognised.[2.] Both camps are adamant that their technique is best. This would seem to be an unnecessary variation in care. We should determine which technique is best and all adopt the superior technique. Superiority should be based on evidence and we should be able to find the evidence to determine which is better. This belief that evidence can always be found to support one practice or another is based on the determinist philosophy that underpins most of modern medicine.

A review of the published literature found some evidence to suggest that TIVA may be superior in some aspects of care but the evidence was indirect and insufficient to justify a change of practice. We then performed a small prospective observational study. These data were also inconclusive and, as with all observational studies, any differences may have been explained by bias or confounding factors. It seemed like the best thing to do was a large clinical trial comparing volatile and TIVA anesthesia for tonsillectomy. The large number of cases and clinical equipoise would imply that such a trial would be ethical and feasible. However when planning the details of such a trial we soon came into difficulty.

The first problem was standardising each technique. There are variations to TIVA and to volatile anesthesia. There are also hybrids where propofol is given at the end of volatile based anesthesia. Use of opioids and alpha2 antagonists varies, as does use of laryngeal mask or endotracheal tube, and whether the airway is removed deep or light (or indeed somewhere in between). There is considerable variation of practice beyond just TIVA versus volatile anesthesia, and it is plausible that any or all these may impact on the superiority of either TIVA or volatile anesthesia.

A “pragmatic trial” would suggest we allow a range of practice to see what the average effect is. An “explanatory” trial would carefully control for all factors which may modify the effect. Both are valid and both have problems in translation. Pragmatic trial results are applicable to situations where the intervention is to be applied broadly across populations, but their limitation is the risk that the intervention may be less effective or even harmful in subpopulations. Clinicians are often wary of applying the results of pragmatic trials to their particular patient – particularly if the pragmatic trial was in a very heterogeneous population. This includes not only different demographic populations but variations in other aspects of management that effectively divide the population too. This hesitancy to trust pragmatic trials is most warranted when it is biologically plausible that the efficacy could vary within the demographic population or with other aspects of management. Sub group analyses of large pragmatic trials can help, but these analyses are often underpowered or run the risk of type one error. There is a common mantra that large pragmatic trials are inherently better, but this is simplistic. Too much heterogeneity in a population can make the pragmatic trial uninterpretable. For example a pragmatic trial may randomise pediatric anesthiologists to compare travel times if driving a car or riding a bike to work. Obviously the outcome will vary considerably with distance travelled, level of fitness, being urban or rural, time of day etc. Explanatory trials provide stronger evidence for particular populations but then the results may again be non-applicable outside that population. Neither trial satisfies everybody. This is known as the Goldilocks problem of trials. Given the substantial and interwoven variation of practice in anesthesia for tonsils, a single large pragmatic trial is unlikely to be definitive. A series of more controlled explanatory trials in various “populations” may provide more useful evidence.

The second problem with designing the tonsil trial was defining the primary outcome. While both camps were adamant that their technique was “best” they had difficulty articulating what they meant by “best”. Which outcome was driving their enthusiasm? Was it emergence delirium, airway complications, time in recovery, pain, vomiting, or simply nurse or carer satisfaction? There was disagreement between and *within* each camp over which of these mattered the most. Trials are difficult to design without a clear primary outcome. Seeking help, the trial was presented at the Australian and New Zealand College of Anaesthetists Clinical Trail Network workshop. Feedback suggested that if it is difficult to identify which amongst disparate outcomes is most problematic then perhaps *none* of them *are* particularly problematic. Or as my old mentor Frank McGowan succinctly put it: “what is the significant clinical problem and meaningful adverse event data driving this trial? What's the critical gap in current knowledge that this will address?”

Clinical trials are expensive and resource intensive. They should be used where they are most valuable in terms of improving important outcomes. What are the important outcomes? Importance

of an outcome is determined by; a) frequency, b) severity and impact, and c) what matters most to patients and families. In general, a substantial body of work still remains to be done to better define the important outcomes in pediatric anesthesia.[3] In our specific TIVA versus volatile for tonsils question, the important outcomes for tonsillectomy have yet to be identified; hence the difficulty in designing the trial.

Once identifying the outcome(s) of importance the next step should be to see which aspects of variation are most likely to be linked to that outcome. This may be determined by results in observational studies or from trials in similar populations, and by understanding the physiology and pharmacology underlying any putative causation. Lastly the population for the trial needs to be carefully chosen. Balancing the well-controlled explanatory versus the broad pragmatic is not a trivial task and is the art of a good trial design. For tonsillectomy and TIVA choosing a number of more controlled explanatory trials may well be the better strategy, which together can better address all the inevitable nuances in practice.

In summary, should variation in care drive our clinical trial agenda? Should we be concerned that half our department use TIVA and half use volatile anesthesia for tonsillectomy? Yes, variation of care should drive our trial agenda, *if* there is evidence of poor outcome *and* the variation could be plausibly linked to a difference in *important* outcomes. However designing the optimal trial to address the variation is never a simple task.

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