School of Thought

How Can Surgical Trials Ask the Best Questions to Advance Care?


The value of data on emerging surgical modalities depends on trial design.

BY CHENGJIE ZHENG, MD, AND PRADEEP Y. RAMULU, MD, MHS, PHD

The number of treatment options for lowering IOP in patients with glaucoma has never been greater. When treating a patient who needs escalation of care, a physician can consider additional eye drops, several types of laser trabeculoplasty, numerous microinvasive glaucoma surgery (MIGS) procedures, or traditional surgeries such as trabeculectomy or tube shunts. Often, many of these options might be considered for the same patient. Data from clinical trials can help us to make these daily clinical decisions, but often these data are limited. What can clinicians look for in clinical trial design to help weigh the data? This article explores some of the elements of trial design that can and should make a difference in our clinical decision-making.

SINGLE-ARM STUDIES

Many therapeutic studies, including studies investigating recently introduced glaucoma surgical procedures, have been single-arm observational studies. Indeed, a recent meta-analysis of MIGS procedures found that, of 30 studies analyzed, nine were randomized controlled trials and 21 were nonrandomized studies.[1] What is the value of these single-arm trials, and are they sufficient to adequately guide our complex decision-making grid?

The relative merits of single-arm and randomized controlled (ie, comparative) trials have perhaps been best analyzed in the field of oncology, in which lower-powered (typically nonrandomized) phase 2 trials are often carried out before larger randomized phase 3 trials are undertaken. Chen et al[2] found that, of all phase 3 randomized controlled trials from 1955 to 2006 that were conducted based on positive phase 2 results, only 24% showed a positive result in the phase 3 study, meaning that single-arm were trials were often not predictive of benefit over standard therapies. Through simulation models, it has been suggested that this failure to confirm occurs from single-arm trials overestimating positive results through overly favorable

AT A GLANCE

- The question of which procedure is more likely to lower a given patient's IOP to a target level and get him or her off medication without inviting complications is best answered by a comparative trial.
- Comparative trials are only helpful if the comparator arms reflect the treatment decisions that physicians encounter in practice.
- Uncertainty about a new procedure can be so crippling that physicians never try new technologies or gain enough experience with them to obtain optimal results.

choices in historical controls, patient populations, and other interinstitutional variables.[3,4]

What does this mean for glaucoma? There are certainly variations between studies in patient population and methodology. Patient populations may differ with regard to severity of disease, baseline IOP, and the use or absence of IOP-lowering medications. Study methods may contain differences in surgical technique, follow-up time, and final endpoints. If baseline IOP in a single-arm study is high, there may be greater opportunity for IOP lowering than for trials that start with a "normal" IOP, skewing the study toward showing a greater effect. If surgeries performed in a study are done only by expert glaucoma surgeons or expert cataract surgeons, this may not translate to general practice across the country. Thus, the degree and likelihood of reported IOP lowering may or may not translate to what a physician observes in practice.

Although these same problems can also affect the results of comparative trials, there is a strong possibility that both treatment groups in a comparative trial will be affected in the same direction. Experienced surgeons will have better results with both surgeries; patients with higher starting IOPs will show a greater absolute reduction in both treatment arms.

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Ultimately, we know that no surgical technique or technology is guaranteed to lower a given patient's IOP to a target level and get him or her off medication. What we'd like to know is which procedure is more likely to do so without inviting complications. This is a question best answered by a comparative trial.

COMPARATIVE TRIALS: CONTROL GROUP ISSUES

Comparative trials are only really helpful if the comparative arms used reflect the treatment decisions we encounter. Therefore, it is important for study designers to consider what the control arm of the study should be.

Often, in comparative trials, a new MIGS procedure is compared with cataract surgery alone. Many such studies have found significant IOP reduction in both the interventional and control arms.[5] Although many MIGS procedures have subsequently been approved for use in conjunction with cataract surgery, most patients who need escalation of glaucoma care may not have a visually significant cataract. Many elderly patients are already pseudophakic, and others have little cataract or enough refractive error that cataract surgery cannot be considered unless one entertains bilateral surgery or other options to minimize postoperative anisometropia. Thus, although cataract

Figure 1. The process of discerning useful data from a prolific research landscape in new surgical techniques for application in clinical practice.

WHEN CONSIDERING A NEW TECHNOLOGY

1. Choose initial patients cautiously, under-promising and hopefully over-delivering results
2. Consider the patient's target IOP carefully
3. Review your results early on, looking for which patients did the best and why
4. Interact with the glaucoma community and ask questions directly to experienced surgeons

surgery alone may be a convenient comparator, it is rarely the *other* option we are considering when deciding how to achieve further IOP lowering.

In a more common clinical scenario, the physician has decided to lower IOP to prevent further visual field damage and is considering whether a MIGS procedure will lower IOP sufficiently and provide an extra degree of safety as compared with traditional surgery such as trabeculectomy. Or perhaps the physician is considering whether to risk surgery earlier using a MIGS procedure as opposed to trying less risky options such as performing laser trabeculoplasty or adding another medication. Unfortunately, the trials conducted to date have not given us information on these types of comparisons, and it is typically unclear which therapeutic option is most likely to give our patients their desired result.

NO COMPARATIVE STUDY: WHAT NOW?

If there is no comparative study to guide our clinical decision-making, we must do our best to extrapolate study results to the patient in our office, although study populations rarely match our own. If the study population has an average baseline IOP of 27 mm Hg, it is likely to have different outcomes compared with a patient with a starting IOP of 18 mm Hg. Are we going to get a percentage decrease in IOP similar to that achieved in the study, or is the final IOP going to be the same regardless of the starting IOP? Are our results going to be different because of the patient's race or ethnicity, degree of disease severity, or other factors that may be atypical? With a new procedure, uncertainty over these questions can be crippling—perhaps so crippling that we never try new technologies or gain enough experience with them to obtain optimal results.

How does one then avoid being the last to adopt a new technology that could revolutionize the field? First, choose initial patients cautiously, under-promising (and hopefully over-delivering) results. Second, consider the patient's target IOP carefully; if he or she requires a target IOP of 12 mm Hg, then a new surgical option with a reported average endpoint IOP of 15 mm Hg is unlikely to be sufficient. Indeed, even if the patient requires a target IOP of 15 mm Hg, surgery will likely fail to meet this target 50% of the time, or perhaps more often if your results are worse than those reported. With these considerations, early cases may often be primary glaucoma patients who don't require a particularly low IOP.

Third, review your results early on. At our institution, we have found it useful to have a single surgeon serve as an early adopter of a new procedure, feed that surgeon cases for which the surgery is appropriate, and ask him or her to analyze the results after the first 24 to 36 cases. There is always a learning curve with new surgical techniques, so keep in mind that results will likely improve. But look for which patients did the best and try to determine why. Only then can technique and patient selection be optimized.

Last, interact with the glaucoma community through meetings, particularly sessions that allow you to watch videos, learn pearls from physicians honestly willing to share their complications and tribulations, and ask questions directly to experienced surgeons. ■

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