Commentary: The superiority of noninferiority

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Perhaps no topic has so captivated the cardiac surgical research imagination as the quest for the perfect method of myocardial preservation. Since the introduction of hypothermia¹ and potassium,² there has been extraordinary progress in the development of safe, reproducible, and readily applicable techniques and solutions. Recent interest has increased in single-dose approaches that facilitate the uninterrupted conduct of complex operations.³ Histidine-tryptophan-ketoglutarate solution (Custodiol HTK; Essential Pharmaceuticals, LLC, Durham, NC), an intracellular cardioplegic solution developed largely for use in transplantation,⁴ has gained popularity as a potentially convenient single-dose approach to myocardial preservation in the absence robust randomized control data on effectiveness.⁵ Into this gap step Vivacqua and colleagues,⁶ with a noninferiority trial in this issue of the *Journal* comparing single-dose Custodiol HTK with repetitive cold blood cardioplegia. Vivacqua and colleagues⁶ are certainly to be congratulated—as difficult as it can be to conduct prospective, randomized, controlled trials in cardiac surgery, the noninferiority trial design introduces another layer of complexity.

Developed to evaluate new therapeutic approaches with similar clinical efficacy but other potential benefits, the noninferiority design is more complex than the more common superiority approach. The null hypothesis states that the experimental treatment is worse than that of the positive control by a prespecified margin, and noninferiority is demonstrated by rejection of that null hypothesis at a prespecified level of statistical significance.⁷ Selection of an appropriate margin is frequently guided by previous prospective, randomized, controlled trials of the active “control” versus placebo. The margin cannot be greater than the smallest effect size for the active treatment that could be expected from such a placebo-controlled trial. Unfortunately, there is no placebo-controlled study that could reasonably test use versus nonuse of cardioplegia. Vivacqua and colleagues,⁶ therefore determined their margin on the basis of a 50% difference in biomarkers.⁸ With these liberal margins of treatment effect, the study end point of

Hypothesis testing in noninferiority trials.

Central Message

Single-dose cardioplegia provides an attractive approach to myocardial protection and warrants careful application of trial methodology to determine effectiveness.

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noninferiority was met. One is left, however, with a troubling question. If cardiac enzyme release is an accurate reflection of myocardial injury, are we really willing to accept a method that results in as much as 49% greater injury to the myocardium? If so, then their power calculation would support a test of noninferiority. Given the nature of cardiac surgical patients for whom we currently care, however, many with reduced ventricular function, myocardial hypertrophy, diabetic vasculopathy, and so on, if one would not accept such a wide margin of injury, then the study is not sufficiently powered. It is certainly true that the actual confidence intervals achieved suggest that a much tighter margin might have been met, but that would have required many more than 55 patients in each arm of the trial. Had the study been performed with a less generous margin, perhaps investigators would have been discovered that 1 in 100 patients has a fatal adverse reaction, or that there is some subset not sufficiently represented for whom this approach does not work well. Given the historical track record of this particular solution, such “random” adverse events do seem unlikely. Noninferior? Maybe. Maybe even probably. Careful application of experimental design will, I hope, inform future more definitive trials.

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